Cochrane Library

Cochrane Database of Systematic Reviews

Probiotics for preventing acute otitis media in children (Review)

Scott AM, Clark J, Julien B, Islam F, Roos K, Grimwood K, Little P, Del Mar CB

Scott AM, Clark J, Julien B, Islam F, Roos K, Grimwood K, Little P, Del Mar CB.
Probiotics for preventing acute otitis media in children.
Cochrane Database of Systematic Reviews 2019, Issue 6. Art. No.: CD012941.
DOI: 10.1002/14651858.CD012941.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Probiotics for preventing acute otitis media in children

Anna M Scott[1], Justin Clark[1], Blair Julien[2], Farhana Islam[2], Kristian Roos[3], Keith Grimwood[4], Paul Little[5], Chris B Del Mar[1]

[1]Centre for Research in Evidence-Based Practice (CREBP), Bond University, Gold Coast, Australia. [2]Bond University, Robina, Australia. [3]ENT Department, Lundby Hospital, Goteborg, Sweden. [4]School of Medicine and Menzies Health Institute Queensland, Griffith University and Departments of Infectious Diseases and Paediatrics, Gold Coast Health, Gold Coast, Australia. [5]Primary Care and Population Sciences, Faculty of Medicine, Aldermoor Health Centre, University of Southampton, Southampton, UK

Contact: Anna M Scott, Centre for Research in Evidence-Based Practice (CREBP), Bond University, 14 University Drive, Gold Coast, Queensland, 4229, Australia. ascott@bond.edu.au.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 6, 2019.

Citation: Scott AM, Clark J, Julien B, Islam F, Roos K, Grimwood K, Little P, Del Mar CB. Probiotics for preventing acute otitis media in children. *Cochrane Database of Systematic Reviews* 2019, Issue 6. Art. No.: CD012941. DOI: 10.1002/14651858.CD012941.pub2.

ABSTRACT

Background

Acute otitis media (AOM), or acute middle ear infection, is one of the most frequently occurring childhood diseases, and the most common reason given for prescribing antibiotics in this age group. Guidelines often recommend antibiotics as first-line treatment for severe AOM. However, antibiotics also lead to antibiotic resistance, so preventing episodes of AOM is an urgent priority.

Objectives

To assess the effects of probiotics to prevent the occurrence and reduce the severity of acute otitis media in children.

Search methods

We searched CENTRAL, PubMed, Embase, and three other databases (October 2018), two trial registers (October 2018), and conducted a backwards and forwards citation analysis (August 2018). We did not apply any language, publication date, or publication status restrictions.

Selection criteria

Randomised controlled trials (RCTs) of children (aged up to 18 years), comparing probiotics with placebo, usual care, or no probiotic.

Data collection and analysis

Two review authors independently assessed the eligibility of trials for inclusion and risk of bias of the included trials, and extracted data using pre-piloted data extraction forms. We analysed dichotomous data as either risk ratio (RR) or odds ratios (OR) and continuous data as mean differences (MD).

Main results

We included 17 RCTs involving 3488 children, of which 16 RCTs were included in the meta-analyses. Of the 16 RCTs that reported the mean age of children, mean age overall was 2.4 years; in 4 RCTs the mean age of children participating in the trial was less than 1 year old; in 2 RCTs the mean age was between 1 and 2 years old; and in 10 RCTs the mean age was older than 2 years. Probiotic strains evaluated by the trials varied, with 11 of the included RCTs evaluating *Lactobacillus*-containing probiotics, and six RCTs evaluating *Streptococcus*-containing probiotics.

The proportion of children (i.e. the number of children in each group) experiencing one or more episodes of AOM during the treatment was lower for those taking probiotics (RR 0.77, 95% confidence interval (CI) 0.63 to 0.93; 16 trials; 2961 participants; number needed to treat for an additional beneficial outcome (NNTB) = 10; moderate-certainty evidence).

Post hoc subgroup analysis found that among children not prone to otitis media, a lower proportion of children receiving probiotics experienced AOM (RR 0.64, 95% CI 0.49 to 0.84; 11 trials; 2227 participants; NNTB = 9; moderate-certainty evidence). However, among children who were otitis prone, there was no difference between probiotic and comparator groups (RR 0.97, 95% CI 0.85 to 1.11; 5 trials; 734 participants; high-certainty evidence). The test for subgroup differences was significant (P = 0.007).

None of the included trials reported on the severity of AOM.

The proportion of children experiencing adverse events did not differ between the probiotic and comparator groups (OR 1.54, 95% CI 0.60 to 3.94; 4 trials; 395 participants; low-certainty evidence).

Probiotics decreased the proportion of children taking antibiotics for any infection (RR 0.66, 95% CI 0.51 to 0.86; 8 trials; 1768 participants; NNTB = 8; moderate-certainty evidence). Test for subgroup differences (use of antibiotic specifically for AOM, use of antibiotic for infections other than AOM) was not significant.

There was no difference in the mean number of school days lost (MD −0.95, 95% CI −2.47 to 0.57; 5 trials; 1280 participants; moderate-certainty evidence). There was no difference between groups in the level of compliance in taking the intervention (RR 1.02, 95% CI 0.99 to 1.05; 5 trials; 990 participants).

Probiotics decreased the proportion of children having other infections (RR 0.75, 95% CI 0.65 to 0.87; 11 trials; 3610 participants; NNTB = 12; moderate-certainty evidence). Test for subgroup differences (acute respiratory infections, gastrointestinal infections) was not significant.

Probiotic strains trialled and their dose, frequency, and duration of administration varied considerably across studies, which likely contributed to the substantial levels of heterogeneity. Sensitivity testing of funnel plots did not reveal publication bias.

Authors' conclusions

Probiotics may prevent AOM in children not prone to AOM, but the inconsistency of the subgroup analyses suggests caution in interpreting these results. Probiotics decreased the proportion of children taking antibiotics for any infection. The proportion of children experiencing adverse events did not differ between the probiotic and comparator groups. The optimal strain, duration, frequency, and timing of probiotic administration still needs to be established.

PLAIN LANGUAGE SUMMARY

Probiotics ('healthy bacteria') for preventing acute middle ear infection in children

Review question

Does taking probiotics (‘healthy bacteria’) prevent children from getting acute middle ear infections?

Background

Acute middle ear infection is very common in childhood. It is caused by bacteria that travel from the upper part of the throat, through canals (called Eustachian tubes), to the middle ear. Symptoms include fever, earache, and occasionally the eardrum may perforate, discharging pus into the ear canal.

Antibiotics are often prescribed for acute middle ear infection, although they have only a modest effect on reducing symptoms. Moreover, excessive antibiotic use leads to antibiotic resistance, making them less effective for these and other infections. Consequently, preventing acute middle ear infection is highly desirable.

Probiotics are often sold as tablets or powders, as a food ingredient (e.g. in yogurt), and even sprayed directly into the throat. However, it is not yet clear whether they prevent acute middle ear infection. We analysed the scientific evidence to answer this question.

Study characteristics and searches

We searched and identified 17 randomised controlled trials (studies in which participants are assigned to one of two or more treatment groups using a random method), published before October 2018. All were conducted in Europe, and collectively included 3488 children. Twelve trials included children who were not prone to acute middle ear infections, whilst five trials included children who were prone to such infections.

Key results

One-third fewer children not prone to acute middle ear infection who took probiotics experienced acute middle ear infections compared to children not taking probiotics. However, probiotics may not benefit children prone to acute middle ear infection. Taking probiotics did not impact on the number of days of school that children missed. None of the studies reported on the impact of probiotics on the severity of acute middle ear infection. There was no difference between the group taking probiotics and the group not taking probiotics in the number of children experiencing adverse events (harms).

Quality of the evidence

The quality (or certainty) of the evidence was generally moderate (meaning that further research may change our estimates) or high (further research is unlikely to change our estimates). However, the trials differed in terms of types of probiotics evaluated, how often and for how long they were taken, and how the trial results were reported.

Summary of findings for the main comparison. Probiotic compared to placebo for preventing acute otitis media in children

Probiotic compared to placebo for preventing acute otitis media in children

Patient or population: children up to age 18 years
Setting: community, primary care, and secondary care
Intervention: any probiotic, delivered by any means
Comparison: comparator

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with probiotic				
Proportion of children with AOM (overall)	Study population 390 per 1000	300 per 1000 (246 to 362)	RR 0.77 (0.63 to 0.93)	2961 (16 RCTs)	⊕⊕⊕⊖ MODERATE[1]	We conducted a post hoc sensitivity analysis by health status (children prone to AOM versus children not prone to AOM). The test for subgroup differences was significant (P = 0.007). The follow-up duration ranged from 20 days to 2 years.
Proportion of children with AOM: children not prone to AOM	Study population 295 per 1000	189 per 1000 (145 to 248)	RR 0.64 (0.49 to 0.84)	2227 (11 RCTs)	⊕⊕⊕⊖ MODERATE[2]	The follow-up duration ranged from 20 days to 2 years.
Proportion of children with AOM: children prone to AOM	Study population 660 per 1000	641 per 1000 (561 to 733)	RR 0.97 (0.85 to 1.11)	734 (5 RCTs)	⊕⊕⊕⊕ HIGH	The follow-up duration ranged from 20 days to 2 years.
Severity of AOM	No data	No data	No data	No data	N/A	None of the included studies reported on this outcome.
Adverse events	Study population 186 per 1000	260 per 1000 (121 to 474)	OR 1.54 (0.60 to 3.94)	395 (4 RCTs)	⊕⊕⊖⊖ LOW[3]	The follow-up duration ranged from 20 days to 2 years.

Time off school for child	--	MD −0.95 days (−2.47 to 0.57)	--	1280 (5 RCTs)	⊕⊕⊕⊖ MODERATE[4]	The follow-up duration ranged from 20 days to 2 years. The median of trial means for the probiotic group was 4.45 days of absence; the median of trial means for the comparator group was 5.8 days of absence.
Difference in the use of antibiotics	Study population		RR 0.66 (0.51 to 0.86)	1768 (8 RCTs)	⊕⊕⊕⊖ MODERATE[5]	The follow-up duration ranged from 20 days to 2 years.
	397 per 1000	262 per 1000 (203 to 342)				
Difference in proportion of children with other infections	Study population		RR 0.75 (0.65 to 0.87)	3610 (11 RCTs)	⊕⊕⊕⊖ MODERATE[6]	The follow-up duration ranged from 20 days to 2 years.
	363 per 1000	272 per 1000 (236 to 316)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

AOM: acute otitis media; **CI:** confidence interval; **MD:** mean difference; **N/A:** not applicable; **OR:** odds ratio; **RCT**: randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[1]Downgraded one level for substantial heterogeneity (72%).
[2]Downgraded one level for moderate/substantial heterogeneity (59%).
[3]Downgraded two levels for imprecision, wide confidence intervals, and small number of participants.
[4]Downgraded one level for moderate heterogeneity (54%).
[5]Downgraded one level for substantial heterogeneity (70%).
[6]Downgraded one level for substantial heterogeneity (64%).

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most common childhood infections. It is characterised by effusion of the middle ear and rapid onset of symptoms such as fever, malaise, ear pain, and, on occasion, otorrhoea (discharge from the ear) (AAP 2013). Although AOM has low mortality, it has a high disease burden (Stool 1989); by two years of age, 70% of children have had at least one episode of AOM, and 20% to 30% of children have experienced three or more episodes (Hatakka 2007b). Globally, the incidence rate (new episodes of AOM per hundred people per year) is estimated at 10.85% (the equivalent of 709 million cases of AOM annually); the incidence rate varies, from a low of 3.64% in Central Europe to 43.37% in central sub-Saharan Africa (Monasta 2012).

Clinical care guidelines for treatment of AOM vary internationally. For mild-moderate cases, 'watchful waiting' has now been adopted in many high-income countries, although this remains infrequent in low-income countries (Tamir 2017). Most guidelines recommend amoxicillin as first-line treatment, with some exceptions: amoxicillin-clavulanate in some high-income countries, penicillin V in Scandinavian countries, whilst other first-line treatments in low-income countries include trimethoprim-sulphamethoxazole, cephalexin, cloxacillin, and others (Tamir 2017). Accordingly, AOM is one of the main reasons given for prescribing antibiotics in children (Hendley 2002). However, the rates of antibiotic prescription for AOM vary internationally, from 56% of consultations for AOM in the Netherlands (Akkerman 2005), to 89% to 95% in Australia and North America, respectively (Froom 2001; McCullough 2017). Antibiotic use leads to antibiotic resistance, therefore there is increased interest in identifying novel means of preventing AOM, especially since randomised clinical trials of pneumococcal and influenza vaccines have demonstrated limited protective efficacy against AOM (Cohen 2013b; Dagan 2016; Fortanier 2014; Hatakka 2007b; Jefferson 2018; Niittynen 2012).

Description of the intervention

The World Health Organization (WHO) defines probiotics as live micro-organisms that confer a health benefit on the host when administered in adequate amounts (FAO-WHO 2006). Micro-organisms used as probiotics include: *Lactobacillus* (e.g. *L acidophilus*, *L fermentum*), *Bifidobacterium* (e.g. *B bifidum*, *B lactis*), *Streptococcus* (e.g. *S thermophiles*) species, and *Saccharomyces* (e.g. *S boulardii*) species (Niittynen 2012). Probiotics are available in multiple forms: as tablets or powders or liquid drops (regulated as dietary supplements), as a food ingredient (e.g. yogurt or kefir) (Wang 2016), or directly applied by spray to the throat (Roos 2001b). While probiotics are not currently routinely used in clinical practice, they can be used by adults and children (Wang 2016), and are not generally believed to have harmful effects in healthy, immunocompetent people (Marteau 2002).

How the intervention might work

Acute otitis media is thought to be caused by pathogenic bacteria entering the middle ear cleft from the nasopharynx via the Eustachian tubes. Probiotics may restore the balance of the normal microbiota (Hatakka 2007b), although the mechanism for this is unclear (Hao 2015); they may stabilise gut microbiota; maintain epithelial cell barrier function; modulate immune function; compete with pathogens for nutrients or adhesion sites on epithelial cell surfaces; produce bacteriocins or other inhibitory substances (Hao 2015; Hatakka 2007b; Niittynen 2012).

Why it is important to do this review

Concern about antibiotic use leading to increased antibiotic resistance has created interest in alternative managements (O'Neill 2014), which include probiotics (Hatakka 2007b). Cochrane Reviews have investigated other interventions for the prevention of otitis media, including xylitol (Azarpazhooh 2016), pneumococcal conjugate vaccines (Fortanier 2014), and influenza vaccines (Norhayati 2017). Another Cochrane Review that addressed probiotics to prevent acute respiratory tract infections did not include trials with AOM on the grounds that otitis-prone children may have immunodeficiencies (Hao 2015).

OBJECTIVES

To assess the effects of probiotics to prevent the occurrence and reduce the severity of acute otitis media in children.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), irrespective of study design (e.g. cluster, parallel, cross-over) and publication type (full text, abstract only, unpublished data).

Types of participants

Children (aged up to 18 years).

We excluded children with the following comorbidities or characteristics: chromosomal and genetic disorders; craniofacial abnormalities, including cleft palate; those taking systemic corticosteroids or with immune deficiency status; and those with cystic fibrosis or primary ciliary dyskinesia.

Types of interventions

We included trials comparing probiotics with placebo or usual care or no probiotic. The probiotics could be of any composition (e.g. powder, drink, spray). Any co-intervention (including antibiotics) applied to both the intervention and control groups could be used.

Types of outcome measures

Primary outcomes

1. Proportion of children with AOM (in each group) (i.e. the number of children experiencing one or more episodes of AOM during the treatment).
2. Severity of AOM.
3. Adverse events (e.g. gastrointestinal side effects).

Secondary outcomes

1. Median duration of AOM episodes (days).
2. Difference in the use of antibiotics (e.g. dose, duration).
3. Time off school (for the child) (e.g. in days or hours).
4. Time off work (for the parent or carer) (e.g. in days or hours).
5. Difference between groups in hearing loss, if AOM occurs.
6. Serous/secretory otitis media.

7. Difference in referrals to a specialist (e.g. for glue ear).
8. Difference in other infections (respiratory and gastrointestinal).
9. Compliance with taking probiotics (e.g. measured by pill count or weight of the spray bottle).
10. Quality of life measures (using any validated quality of life measure).
11. Difference in use of other treatments (e.g. differences in dosage of analgesics, decongestants).

Search methods for identification of studies

Electronic searches

We searched the following bibliographic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 9, September), which includes the Cochrane Acute Respiratory Infections Group Specialised Register, in the Cochrane Library (searched 4 October 2018);
2. PubMed (1946 to 4 October 2018);
3. Embase Elsevier (1947 to 4 October 2018);
4. CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature, 1982 to 4 October 2018);
5. LILACS (Latin American and Caribbean Health Science Information database, 1982 to 4 October 2018); and
6. Web of Science (1900 to 4 October 2018).

We searched the following trial registries:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (searched 10 October 2018); and
2. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) (searched 10 October 2018).

We used the search strategies described in Appendix 1 to search the bibliographic databases. Where appropriate, these were combined with the Cochrane Highly Sensitive Search Strategy for randomised trials: sensitivity and precision-maximising version (2008 revision) (Lefebvre 2011). We did not impose any language, publication date, or publication status restrictions.

We used the search strategies described in Appendix 2 to search ClinicalTrials.gov and the WHO ICTRP to identify published registered trials, as well as ongoing trials.

We conducted a backwards (cited) and forwards (citing) citation analyses on all included trials in Web of Science (28 August 2018). As we identified no additional trials, we did not carry out the use of the similar article feature in PubMed and the shared citation matcher in Web of Science.

Searching other resources

We contacted experts in the field to identify additional unpublished materials, however as no relevant unpublished completed trials were identified, we did not need to contact trial investigators for unpublished data.

Data collection and analysis

Selection of studies

Two review authors (AMS and JC, AMS and FI, or AMS and BJ) independently screened the titles and abstracts identified as a result of the search for potentially relevant trials. We retrieved the full-text study reports/publication of all studies deemed potentially relevant, and two review authors (AMS and JC, AMS and FI, or AMS and BJ) independently screened the full texts and identified trials for inclusion, and identified and recorded reasons for exclusion of the ineligible trials. Any disagreements were resolved through discussion or by consulting a third review (CDM) author when necessary. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009). We did not impose any language restrictions.

Data extraction and management

We used a data collection form for study characteristics and outcome data that had been piloted on two trials in the review. Two review authors (AMS and FI, or AMS and BJ) independently extracted the following study characteristics from the included trials.

1. Methods: study location, study design, study objective, study duration.
2. Participants: N, type of participants, mean age, age range, gender, comorbidities, number of previous episodes of otitis media, diagnostic criteria.
3. Interventions: probiotic type, duration, dose, comparison, other permitted interventions (e.g. concomitant analgesics, decongestants), other prohibited interventions (e.g. analgesics, decongestants).
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

We noted in the Characteristics of included studies table if outcome data were not reported in a useable way. Any disagreements were resolved by consensus or by involving a third review author (CDM). One review author (AMS) transferred data into the Review Manager 5 file (RevMan 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (CDM) also conducted a spot-check of study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (AMS and FI, or AMS and BJ) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion or by involving another review author (CDM). We assessed risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.

3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We graded each potential source of bias as high, low, or unclear, and provided a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We summarised the 'Risk of bias' judgements across different trials for each of the domains listed. When considering treatment effects, we took into account the risk of bias for the trials that contributed to that outcome.

Assessment of bias in conducting the systematic review

We conducted the review according to our published protocol (Scott 2018), and reported any deviations from it in the Differences between protocol and review section of the review.

Measures of treatment effect

One review author (AMS) entered the outcome data for each study into the data tables in Review Manager 5 to calculate the treatment effects (RevMan 2014). We analysed dichotomous data as either risk ratio (RR) or odds ratios (OR) and continuous data as mean differences (MD).

We calculated the number needed to treat for an additional beneficial outcome (NNTB) in the following manner: NNTB = 1/ARR, where AAR = absolute risk reduction, that is the absolute difference between the event rate in the untreated (comparator) and treated (probiotic) groups.

We undertook meta-analyses only where this was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense. If meta-analysis was possible, we used a random-effects model due to high heterogeneity of the included trials.

Unit of analysis issues

We used the participant as the unit of analysis; one cluster-RCT met our inclusion criteria (Stecksen-Blicks 2009), but it reported individual data, permitting the use of participant as the unit of analysis. Nocerino 2017 was a three-armed trial with two probiotics arms. We combined the probiotics arms to form one intervention group for the meta-analysis.

Dealing with missing data

We intended to contact investigators or study sponsors to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was identified as abstract only), however we included no incomplete or abstract-only trials in the review.

Where outcome data for standard deviations were missing, we calculated them from 95% confidence intervals (where available) according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), or from the range data (Hozo 2005).

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity amongst the trials in each analysis. If we identified substantial heterogeneity and there were sufficient data, we reported the heterogeneity and explored possible causes for it by subgroup analysis (e.g. see Analyses 1.1.1, 1.1.2, 1.1.3). We considered an I^2 statistic value of 0% to 40% as low heterogeneity; 41% to 60% as moderate heterogeneity; 61% to 90% as substantial heterogeneity; and over 91% as considerable heterogeneity (Higgins 2011).

Assessment of reporting biases

As we were able to pool more than 10 trials, we created a funnel plot to explore possible small-study and publication bias.

Data synthesis

We pooled data from trials we judged to be clinically homogeneous using Review Manager 5 (RevMan 2014). Where three or more trials provided useable data in any single comparison, we performed a meta-analysis. We had expected sizeable heterogeneity in terms of populations, probiotics studied, etc., which materialised, therefore we used the random-effects model. Where the volume of evidence was insufficient to perform a meta-analysis, we reported outcomes in a narrative format.

GRADE and 'Summary of findings' table

We created a 'Summary of findings' table using the following outcomes: proportion of children with AOM; proportion of children with AOM among children not prone to AOM; proportion of children with AOM among children prone to AOM; severity of AOM; adverse events; time off school; antibiotic use; and proportion of children with other infections. We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality (certainty) of a body of evidence as it related to the trials that contributed data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to down- or upgrade the quality (certainty) of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We conducted the following subgroup analyses:

1. proportion of children with AOM by child's health status (AOM-prone versus not);
2. proportion of children with AOM by strain of probiotic (*Lactobacillus*-containing versus *Streptococcus*-containing);
3. proportion of children using antibiotics (use for AOM versus use for infections other than AOM); and
4. proportion of children with other infections (acute respiratory infections versus gastrointestinal infections).

We used the Chi^2 test to test for subgroup interactions in Review Manager 5 (RevMan 2014).

Sensitivity analysis

We did not conduct any sensitivity analyses, as only a single included study had two domains rated as at high risk of bias (Di Pierro 2016).

RESULTS

Description of studies

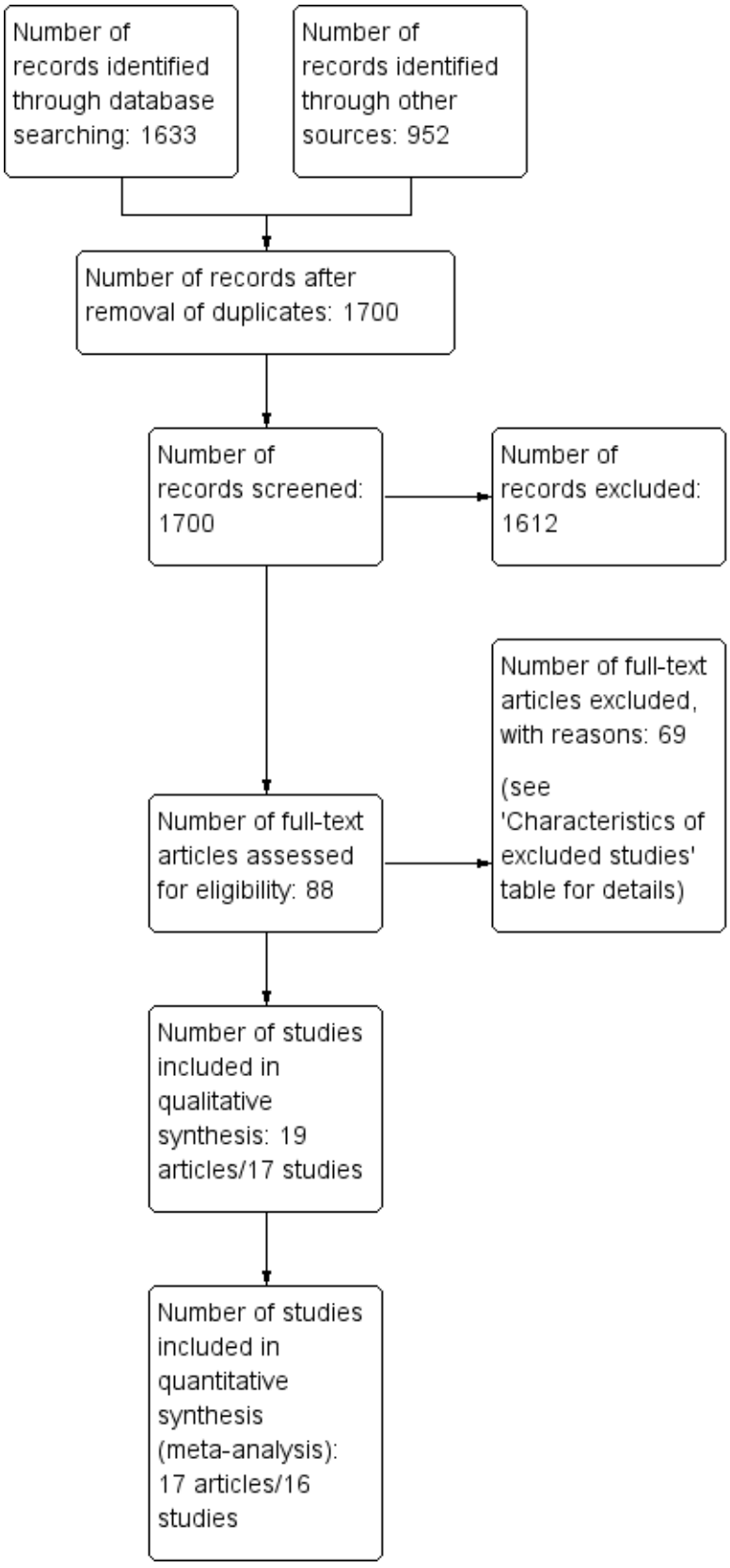
Results of the search

We searched six databases (see Electronic searches) and retrieved 1633 records. A backwards (screening of the reference lists) and forwards citation analysis, undertaken in Web of Science on our initial list of included trials, retrieved 952 records for screening, for a total of 2585 records for screening. Our search of two clinical trial registers identified 25 further trials.

After removal of duplicates (from both the search and the citation analysis), a total of 1700 records remained for screening. We excluded 1612 records based on title and abstract. We obtained the full texts of the remaining 88 records. We excluded 69 trials (see Characteristics of excluded studies table). From the 25 clinical trial register results, we identified nine ongoing trials. No trials were awaiting classification.

We included 17 trials reported in 19 references (see Characteristics of included studies table). For a detailed description of our screening process, see the study flow diagram in Figure 1. All included trials came from the original search; the citation analysis and search of trial registries identified no additional trials.

Figure 1. Study flow diagram.



Included studies

We included 19 references that reported on 17 randomised clinical trials. Two trials, Maldonado 2012; Taipale 2011, also reported two- or three-year follow-up data, respectively (Maldonado 2015; Taipale 2016).

Study design

Sixteen RCTs had a two-arm parallel design, and one RCT had a three-arm parallel design (Nocerino 2017). Sixteen RCTs randomised by individual, whilst one RCT was a cluster-randomised study, but also reported numbers for individuals (Stecksen-Blicks 2009).

Participants

All 17 included RCTs involved children. The mean (or median where reported instead) age ranged from one-month-old infants, in Taipale 2011, to 17.5-year-olds, in Di Nardo 2014. The trials included a total of 3488 participants, all of whom were children (aged < 18 years old).

Five RCTs reported on children prone to otitis (Cohen 2013a; Hatakka 2007a; Marchisio 2015; Roos 2001a; Tano 2002), whilst the remaining RCTs reported on children not prone to otitis. The definition of 'otitis-prone' was not clear and may have involved a subjective element.

All of the included trials were performed in Europe: two in Croatia (Hojsak 2010a; Hojsak 2016); four in Finland (Hatakka 2001a; Hatakka 2007a; Rautava 2009; Taipale 2011/Taipale 2016); one in France (Cohen 2013a); five in Italy (Corsello 2017; Di Nardo 2014; Di Pierro 2016; Marchisio 2015; Nocerino 2017); one in Russia (Karpova 2015); one in Spain (Maldonado 2012/Maldonado 2015); and three in Sweden (Roos 2001a; Stecksen-Blicks 2009; Tano 2002).

Interventions

Two trials included synbiotics, that is a combination of prebiotic and probiotic (Cohen 2013a; Maldonado 2012/Maldonado 2015); the remaining trials tested probiotics consisting of single or multiple bacterial strains. Eleven RCTs evaluated *Lactobacillus*-containing probiotics (Corsello 2017; Di Nardo 2014; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Maldonado 2012/Maldonado 2015; Nocerino 2017; Rautava 2009; Stecksen-Blicks 2009; Taipale 2011/Taipale 2016); six RCTs evaluated *Streptococcus*-containing probiotics (Cohen 2013a; Di Pierro 2016; Karpova 2015; Marchisio 2015; Roos 2001a; Tano 2002).

The probiotics were administered as powder or drops dissolved in a liquid (e.g. milk or water) in nine RCTs (Cohen 2013a; Corsello 2017; Di Nardo 2014; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Maldonado 2012/Maldonado 2015; Nocerino 2017; Stecksen-Blicks 2009); as capsule or tablet in four RCTs (Di Pierro 2016; Hatakka 2007a; Rautava 2009; Taipale 2011/Taipale 2016); and as a spray in four RCTs (Karpova 2015; Marchisio 2015; Roos 2001a; Tano 2002).

Duration of administration of the probiotic ranged from 20 days, in Roos 2001a, to two years, in Taipale 2016.

Two-arm trials compared probiotic to placebo (15 RCTs) or to untreated group (one RCT; Di Pierro 2016); one three-arm trial compared two probiotic groups to placebo (Nocerino 2017).

Outcome measures

Primary outcomes

Outcome measures were reported in a variety of ways. The primary outcome, proportion of children with AOM, was reported by all 17 trials, most frequently as the number of children with AOM in each group (Cohen 2013a; Corsello 2017; Di Nardo 2014; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Karpova 2015; Marchisio 2015; Nocerino 2017; Rautava 2009; Roos 2001a; Taipale 2011/Taipale 2016; Tano 2002), although some trials reported the number of AOM events in each group, Maldonado 2012/Maldonado 2015, or the mean number of days with otitis media in each group (Stecksen-Blicks 2009).

No trials reported on severity of AOM.

Fourteen RCTs reported on adverse events, most often narratively. Eight trials stated that no adverse events were reported (Corsello 2017; Di Pierro 2016; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Maldonado 2012; Nocerino 2017; Stecksen-Blicks 2009); two trials reported the number of events in each group (Cohen 2013a; Tano 2002); and four trials reported the number of children with events in each group (Marchisio 2015; Rautava 2009; Roos 2001a; Taipale 2011/Taipale 2016).

Secondary outcomes

Only one study reported median duration of AOM episodes (Hatakka 2007a), which reported on the median duration and interquartile range of the AOM episodes in each group.

Five trials reported on difference between groups in the use of antibiotics specifically for AOM (Cohen 2013a; Hojsak 2010a; Karpova 2015; Marchisio 2015; Roos 2001a), either as the number of antibiotic courses in each group, Cohen 2013a, or as the number of children treated with antibiotics for AOM in each group (Hojsak 2010a; Karpova 2015; Marchisio 2015; Roos 2001a). Nine trials reported on difference in the use of antibiotics more generally, for any infection, as the number of antimicrobial treatments or prescriptions per child in each group (Hatakka 2007a; Hojsak 2016; Maldonado 2012); the number of children who received antibiotics in each group (Corsello 2017; Hatakka 2001a; Nocerino 2017; Rautava 2009; Taipale 2011); or the mean number of days with antibiotic treatment (Stecksen-Blicks 2009).

Five trials reported on time off school for the child, as the mean number of days of absence from school or day care (Corsello 2017; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Stecksen-Blicks 2009).

One study reported on time off work for the parent or carer (Corsello 2017), as the mean number of lost days of work for parents.

None of the included trials reported on difference between groups in hearing loss if AOM occurs.

Two trials reported on serous/secretory otitis media (Rautava 2009; Roos 2001a). One study reported on the number of children in each group with secretory otitis media at their last visit (Roos 2001a), and one reported on the number of children in each group requiring tympanostomies to prevent recurrent AOM or to treat secretory otitis media (Rautava 2009).

None of the included trials reported on difference in referrals to specialists.

Difference in other infections was reported in terms of reduction in acute respiratory infections and reductions in gastrointestinal (GI) infections. Fifteen trials reported on difference in respiratory infections, as: mean number of respiratory infections or episodes in each group (Cohen 2013a; Di Nardo 2014; Hatakka 2007a; Maldonado 2012/Maldonado 2015; Tano 2002); number of children with respiratory infections (Corsello 2017; Di Pierro 2016; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Karpova 2015; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016); or the mean number of days with respiratory symptoms (Stecksen-Blicks 2009). Eleven trials reported on difference in GI infections, as: the number of children with GI infections in each group (Cohen 2013a; Corsello 2017; Hojsak 2010a; Hojsak 2016; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016); the number of GI infections in each group (Di Nardo 2014; Maldonado 2012/Maldonado 2015); or the mean number of days with GI symptoms (Hatakka 2001a; Stecksen-Blicks 2009).

Thirteen trials reported on compliance with taking probiotics, as: the number of capsules eaten (Hatakka 2007a); the number of children complying or not complying with treatment (Cohen 2013a; Hojsak 2010a; Hojsak 2016; Marchisio 2015; Taipale 2011); the percentage of days during which consumption exceeded a prespecified amount (Hatakka 2001a); or narratively, for example by stating that the compliance was "good" or the treatment was "well-received" (Corsello 2017; Di Pierro 2016; Maldonado 2012; Nocerino 2017; Stecksen-Blicks 2009; Taipale 2011).

One study reported on quality of life measures (Hatakka 2001a), which reported a mean total symptom score for both groups (measuring the overall burden of symptoms on a scale of 0 to 9).

Three trials reported on difference in the use of other treatments (Corsello 2017; Karpova 2015; Nocerino 2017), as the number of children consuming corticosteroids and antipyretics, in Corsello 2017 and Nocerino 2017, or the number of prescriptions for corticosteroids, in Karpova 2015, in each group.

Study funding sources

Funding sources for the included studies are reported in the Characteristics of included studies table.

Two studies did not report funding (Di Pierro 2016; Karpova 2015).

Eight studies were funded at least partially (either financially or in-kind, e.g. by providing formula or probiotic) by manufacturers of probiotic or formula, but the role of the sponsor in the design, analysis, interpretation, or write-up of the study was not stated (Cohen 2013a; Hatakka 2001a; Hatakka 2007a; Hojsak 2016; Maldonado 2012; Marchisio 2015; Stecksen-Blicks 2009; Tano 2002). Three studies reported funding at least partially (either financially or in-kind, e.g. by providing formula or probiotic) by manufacturers of probiotic or formula, and reported at least some sponsor involvement in study design, analysis, interpretation, or write-up (Maldonado 2015; Taipale 2011; Taipale 2016).

One study was funded by non-industry funders, but the role of the sponsor was unclear (Roos 2001a).

Five studies reported funding at least partially by manufacturers and explicitly stated that the funder had no role in the design, analysis, interpretation, or write-up of the study (Corsello 2017; Di Nardo 2014; Hojsak 2010a; Nocerino 2017; Rautava 2009).

Excluded studies

We excluded 70 trials (Figure 1). The reasons for their exclusion are provided in the Characteristics of excluded studies table.

Risk of bias in included studies

The overall risk of bias of the included trials (Characteristics of included studies table) is presented graphically in Figure 2 and Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

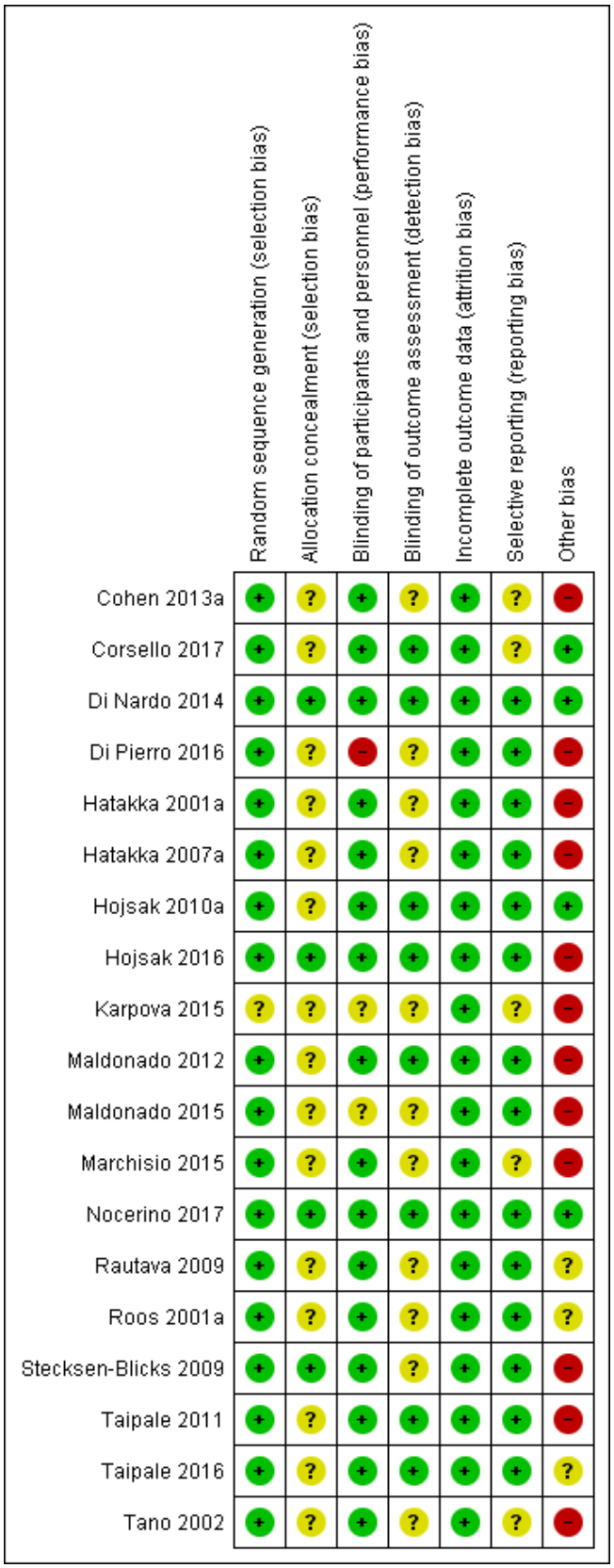
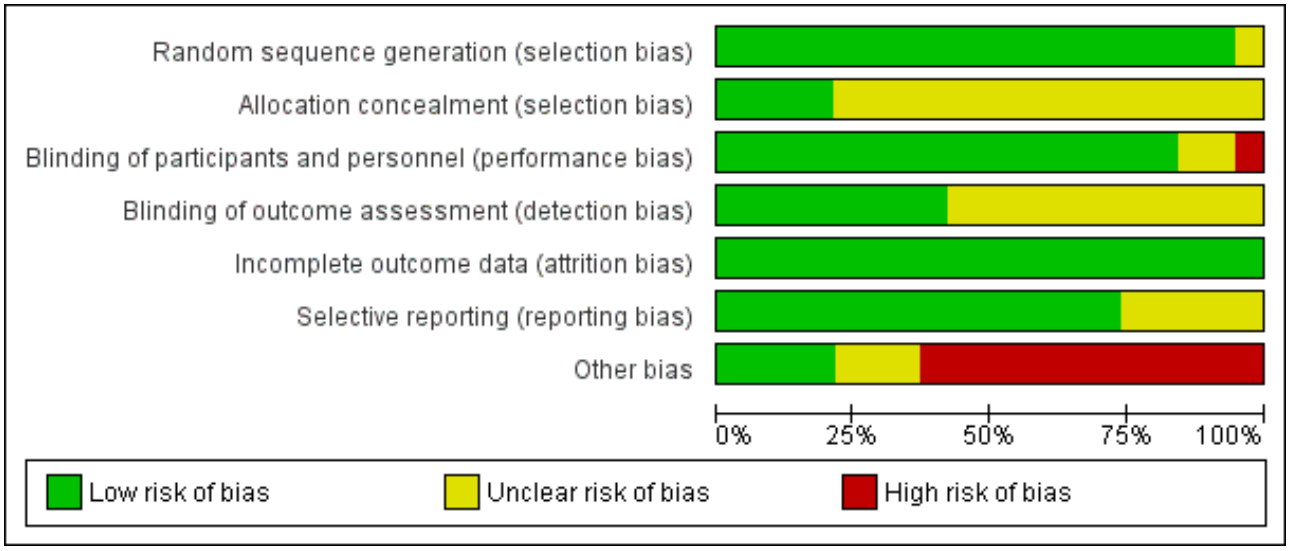


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sixteen trials clearly described random sequence generation (Cohen 2013a; Corsello 2017; Di Nardo 2014; Di Pierro 2016; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Maldonado 2012/Maldonado 2015; Marchisio 2015; Nocerino 2017; Rautava 2009; Roos 2001a; Stecksen-Blicks 2009; Taipale 2011/Taipale 2016; Tano 2002). One study was described as randomised, but the method of randomisation was not described, and a table of baseline characteristics to permit evaluation of whether randomisation worked was not provided (Karpova 2015)

Four trials described allocation concealment (Di Nardo 2014; Hojsak 2016; Nocerino 2017; Stecksen-Blicks 2009). The remaining 13 trials did not describe whether allocation was concealed (Cohen 2013a; Corsello 2017; Di Pierro 2016; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Karpova 2015; Maldonado 2012/Maldonado 2015; Marchisio 2015; Rautava 2009; Roos 2001a; Taipale 2011/Taipale 2016; Tano 2002).

Blinding

Fourteen trials were double-blinded (Cohen 2013a; Corsello 2017; Di Nardo 2014; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Marchisio 2015; Nocerino 2017; Rautava 2009; Roos 2001a; Stecksen-Blicks 2009; Taipale 2011/Taipale 2016; Tano 2002). One study was double-blinded (Maldonado 2012), but it was not clear whether its three-year follow-up was also double-blinded (Maldonado 2015). One study did not clearly report blinding of participants and personnel (Karpova 2015). One study compared probiotic to no treatment and was thus considered unlikely to be blinded (Di Pierro 2016).

Blinding of outcome assessor occurred in six trials (Corsello 2017; Di Nardo 2014; Hojsak 2010a; Hojsak 2016; Nocerino 2017; Taipale 2011/Taipale 2016). In one study the outcome assessors were blinded (Maldonado 2012), but it was unclear whether this was also the case for the three-year follow-up (Maldonado 2015). Blinding was unclear in the remaining 10 trials (Cohen 2013a; Di Pierro 2016; Hatakka 2001a; Hatakka 2007a; Karpova 2015; Marchisio 2015; Rautava 2009; Roos 2001a; Stecksen-Blicks 2009; Tano 2002).

Incomplete outcome data

Sixteen trials reported attrition in both arms with reasons (Cohen 2013a; Di Nardo 2014; Di Pierro 2016; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Karpova 2015; Maldonado 2012/Maldonado 2015; Marchisio 2015; Nocerino 2017; Rautava 2009; Roos 2001a; Stecksen-Blicks 2009; Taipale 2011/Taipale 2016; Tano 2002). One study reported the attrition for both arms but did not provide reasons for it (Corsello 2017); however, as the attrition was less than 20% in both arms, we judged risk of bias to be low.

Selective reporting

We considered whether the trials reported all of the primary and secondary outcomes specified in their methods sections. We judged 12 trials as at low risk of bias (all prespecified outcomes were reported) (Di Nardo 2014; Di Pierro 2016; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Maldonado 2012/Maldonado 2015; Nocerino 2017; Rautava 2009; Roos 2001a; Stecksen-Blicks 2009; Taipale 2011/Taipale 2016). We assessed five trials as at unclear risk of bias for this domain either because one of the outcomes was unreported (Cohen 2013a; Corsello 2017; Karpova 2015), or because it was not clear which outcomes were primary or secondary (Marchisio 2015; Tano 2002).

Other potential sources of bias

We judged four trials at low risk of other bias (Corsello 2017; Di Nardo 2014; Hojsak 2010a; Nocerino 2017). Three trials were judged at unclear risk of other bias due either to absence of information about or an unclear statement of authors' conflicts of interest (Rautava 2009; Roos 2001a), or failure to report their funding source (Taipale 2016). We assessed 12 trials as at high risk of other bias due to authors' employment with study funder, undeclared conflict of interest, and unstated role of the funder in the study design, analysis, interpretation, and manuscript writing (Cohen 2013a; Di Pierro 2016; Hatakka 2001a; Hatakka 2007a; Hojsak 2016; Karpova

2015; Maldonado 2012/Maldonado 2015; Marchisio 2015; Stecksen-Blicks 2009; Taipale 2011; Tano 2002).

Effects of interventions

See: **Summary of findings for the main comparison** Probiotic compared to placebo for preventing acute otitis media in children

Primary outcomes

1. Proportion of children with AOM

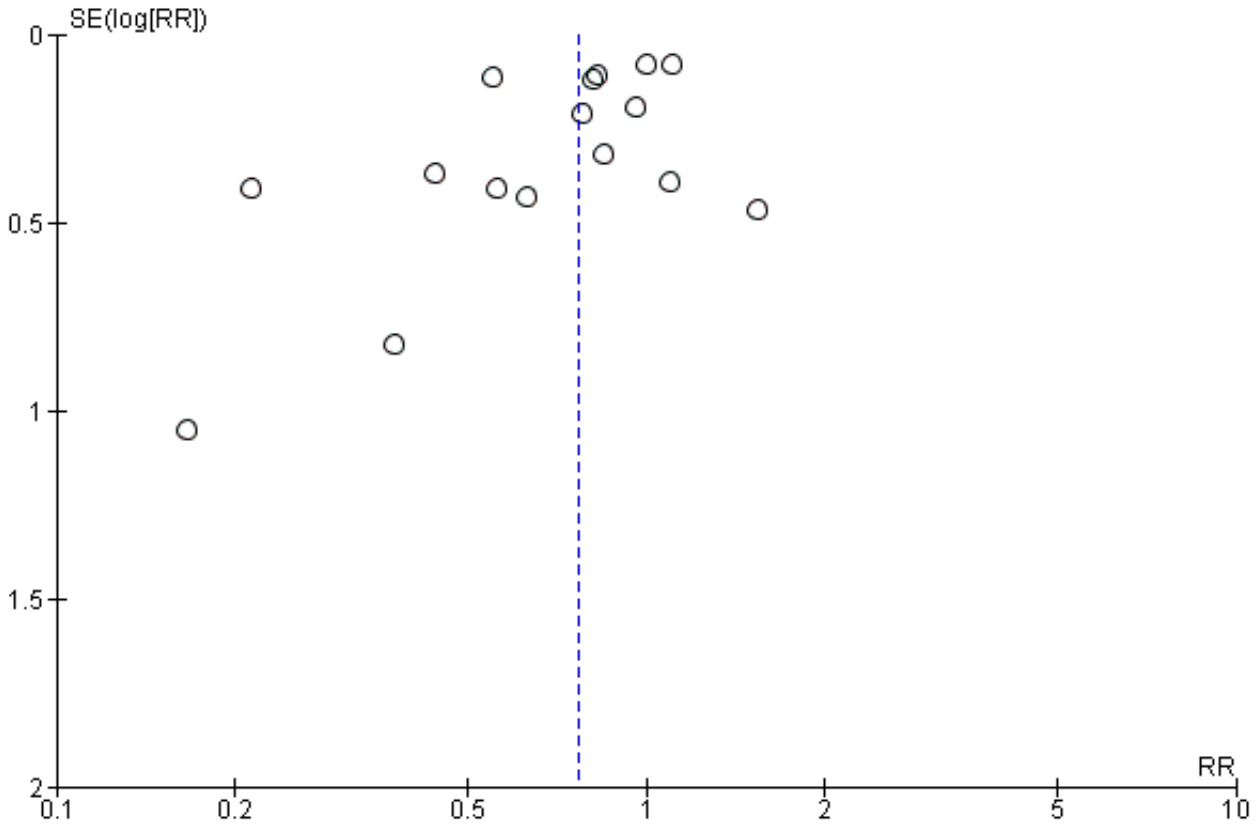
All 17 RCTs reported on this outcome. Two trials, Maldonado 2012/Maldonado 2015; Stecksen-Blicks 2009, could not be pooled with the other 15 trials. Maldonado 2012/Maldonado 2015 reported the number of AOM events in each group, rather than the number of children with AOM events in each group. The difference between groups in the number of AOM events was not significant. Stecksen-Blicks 2009 reported the mean number of days with otitis media; the difference between groups was significant and favoured probiotics: 0.5 days (standard deviation (SD) 2.2) in the probiotic group versus 1.0 (SD 2.7) days in the comparator group, P = 0.003.

We pooled 16 RCTs in three meta-analyses (Cohen 2013a; Corsello 2017; Di Nardo 2014; Di Pierro 2016; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Karpova 2015; Marchisio 2015; Nocerino 2017; Rautava 2009; Roos 2001a; Taipale 2011; Taipale 2016; Tano 2002).

A meta-analysis of 16 RCTs showed that a smaller proportion of children taking probiotics experienced AOM (risk ratio (RR) 0.77, 95% confidence interval (CI) 0.63 to 0.93; P = 0.006; number needed to treat for an additional beneficial outcome (NNTB) = 10; I^2 = 72%; moderate-certainty evidence; Analysis 1.1).

The funnel plot revealed asymmetry (Figure 4). We explored the asymmetry by removing from the analysis two studies whose standard error was above 0.5 (Di Nardo 2014; Karpova 2015). Their removal restored symmetry to the funnel plot, but only slightly changed the effect estimate (RR 0.78, 95% CI 0.65 to 0.95; I^2 = 73%; P = 0.01).

Figure 4. Funnel plot of comparison: 1 Probiotics versus placebo or usual care, outcome: 1.1 Proportion of children with AOM (overall).



A meta-analysis subgrouping the trials into those that included children who were otitis-prone, Cohen 2013a; Hatakka 2007a; Marchisio 2015; Roos 2001a; Tano 2002, and those that included children who were not otitis-prone, Corsello 2017; Di Nardo 2014; Di Pierro 2016; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Karpova 2015; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016, was not pre-planned but was possible due to sufficient data. The meta-analysis showed no significant difference between probiotics and comparator for otitis-prone children (RR 0.97, 95% CI 0.85 to 1.11; I^2 = 32%; P = 0.64). Children who were not prone to otitis media, however, benefited from probiotics, as a smaller proportion experienced AOM (RR 0.64, 95% CI 0.49 to 0.84; I^2 = 59%; P = 0.001; NNTB = 9; Analysis 1.2; Summary of findings for the main

comparison). The test for subgroup differences was significant (P = 0.007).

A meta-analysis subgrouping the trials into those that evaluated *Lactobacillus*-containing probiotics, Corsello 2017; Di Nardo 2014; Hatakka 2001a; Hatakka 2007a; Hojsak 2010a; Hojsak 2016; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016; Tano 2002, and those that evaluated *Streptococcus*-containing probiotics, Cohen 2013a; Di Pierro 2016; Karpova 2015; Marchisio 2015; Roos 2001a; Tano 2002, showed that *Lactobacillus*-containing probiotics significantly decreased the proportion of children with AOM (RR 0.72, 95% CI 0.54 to 0.98; I^2 = 72%; P = 0.04; NNTB = 13), but this was not the case for *Streptococcus*-containing probiotics (RR 0.78, 95% CI 0.60 to 1.02; I^2 = 74%; P = 0.07). The test for subgroup differences was not significant (P = 0.70) (Analysis 1.3).

2. Severity of AOM

None of the included trials reported on the severity of AOM.

3. Adverse events

Fourteen trials reported on adverse events.

Eight trials reported on adverse events narratively, all stating that no adverse events were reported (Corsello 2017; Di Pierro 2016; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Maldonado 2012; Nocerino 2017; Stecksen-Blicks 2009).

Two trials reported the number of adverse events in the probiotic and comparator groups (Cohen 2013a; Tano 2002). Cohen 2013a reported five adverse events (lack of appetite for milk, regurgitation, dry skin, chronic diarrhoea, and abdominal pain) as likely to have been related to the study; four were in the probiotic group and one was in the comparator group, although it was unclear which event occurred in which group. Tano 2002 reported the following adverse events: rhinitis, cough, rash, nosebleed, and vomiting. The total number of adverse events in the placebo group (n = 5) was higher than in the probiotic group (n = 4), P values were not reported.

Four trials reported on the number of children with adverse events in each group (Marchisio 2015; Rautava 2009; Roos 2001a; Taipale 2011/Taipale 2016). As data from Taipale 2016 reiterate data from Taipale 2011, this study was not pooled in order to avoid double-counting; the remaining trials were pooled. The results showed no significant difference between groups in the number of children with adverse events (odds ratio (OR) 1.54, 95% CI 0.60 to 3.94; P = 0.37; low-certainty evidence; Analysis 1.4; Summary of findings for the main comparison).

Secondary outcomes

1. Median duration of AOM episodes

One trial reported on the median duration of AOM episodes (Hatakka 2007a), finding that the median duration of an AOM episode among children taking probiotics was 5.6 days (interquartile range (IQR) 3.5 to 9.4 days), whilst among children taking placebo it was 6.0 days (IQR 4.0 to 10.5 days). The difference between groups was not significant.

2. Difference in the use of antibiotics

Eight trials reported data that could be pooled (Corsello 2017; Hatakka 2001a; Hojsak 2016; Karpova 2015; Marchisio 2015; Nocerino 2017; Rautava 2009; Taipale 2011); the pooled data overall favoured the probiotic group (RR 0.66, 95% CI 0.51 to 0.86; P = 0.002; NNTB = 8; I^2 = 70%; moderate-certainty evidence; Analysis 1.5; Summary of findings for the main comparison).

There were sufficient data to perform subgroup analyses that were not prespecified in the protocol: use of antibiotics for AOM specifically, and use of antibiotics more generally. However, the test for subgroup differences was not significant (P = 0.96).

Difference between groups in the use of antibiotics was reported specifically for AOM as either the number of antibiotic courses for AOM in each group, in Cohen 2013a, or as the number of children treated with antibiotics for AOM, in Hojsak 2010a; Karpova 2015; Marchisio 2015; Roos 2001a. We pooled the data from the latter studies, excepting the Roos 2001a study, where antibiotics were part of the intervention in both groups. Pooled data showed no difference between groups (RR 0.63, 95% CI 0.30 to 1.32; P = 0.22; I^2 = 58%; moderate-certainty evidence). Data from Cohen 2013a were not pooled but showed no significant difference between groups in the number of antibiotic courses (242 courses per 112 children in the probiotic group versus 226 courses per 112 children in the comparator group; P = 0.45; Analysis 1.5)

Nine trials reported the difference in the use of antibiotics for any infection (other than AOM), as follows: the number of antimicrobial treatments or prescriptions per child (Hatakka 2007a; Hojsak 2016; Maldonado 2012); the number of children who received antibiotics in each group (Corsello 2017; Hatakka 2001a; Nocerino 2017; Rautava 2009; Taipale 2011); or the mean number of days with antibiotic treatment in each group (Stecksen-Blicks 2009). Data on the number of children receiving antibiotics in each group were pooled, and favoured the probiotic group (RR 0.65, 95% CI 0.45 to 0.92; P = 0.01; NNTB = 6; I^2 = 77%; moderate-certainty evidence; Analysis 1.5). The studies that could not be pooled all showed no significant difference in the use of antibiotics between probiotic and comparator groups (Hatakka 2007a; Hojsak 2016; Maldonado 2012; Stecksen-Blicks 2009).

However, it is worth noting that effect size estimates for the two subgroups (use of antibiotic for AOM, use of antibiotic for infections other than AOM) are very similar, so it is possible that the non-significant finding for the former is due to underpowering.

3. Time off school for the child

Five trials reported on the mean number of days of children's absence from school or day care in each group (Corsello 2017; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Stecksen-Blicks 2009). Pooled data showed the difference between groups was not significant (mean difference (MD) −0.95 days, 95% CI −2.47 to 0.57; P = 0.22; I^2 = 54%; Analysis 1.6).

4. Time off work for the parent or carer

One trial reported on time off work for the child's parent or carer (Corsello 2017). The mean number of lost workdays was significantly lower in the probiotic group (0.6 days, 95% CI 0.2 to 1.0) than in the comparator group (3.3 days, 95% CI 1.1 to 5.5).

5. Difference between groups in hearing loss, if AOM occurs

None of the included trials reported on the difference between groups in hearing loss.

6. Serous/secretory otitis media

Two trials reported on this outcome, one directly, Roos 2001a, and one indirectly, Rautava 2009.

Roos 2001a reported on the number of children with secretory otitis media at last study visit, finding that fewer children in the probiotic group had serous otitis media (19% versus 27%). Rautava 2009 reported on rates of tympanostomy that were performed to either prevent recurrent AOM or to treat secretory otitis media: 0% of children in the probiotic group and 10% in the comparator group required tympanostomy, but the difference was not significant (P = 0.07).

7. Difference in referrals to a specialist

None of the included trials reported on referrals to a specialist.

8. Difference in other infections

Overall, a smaller proportion of children in the probiotic group had infections (RR 0.75, 95% CI 0.65 to 0.87; P < 0.001; NNTB = 12; I^2 = 64%; Analysis 1.7; Summary of findings for the main comparison).

There were sufficient data to perform the following subgroup analyses not prespecified in the protocol: reduction in acute respiratory infections and reduction in GI infections.

Fifteen trials reported on difference in acute respiratory infections, as follows: mean number of days with respiratory symptoms in each group (Stecksen-Blicks 2009); mean number of respiratory infections or episodes in each group (Cohen 2013a; Di Nardo 2014; Hatakka 2007a; Maldonado 2012/Maldonado 2015; Tano 2002); or number of children with respiratory infections in each group (Corsello 2017; Di Pierro 2016; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Karpova 2015; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016).

The mean number of days with respiratory symptoms was lower in the comparator group than in the probiotic group (9.8 days versus 15.4 days, respectively) (Stecksen-Blicks 2009).

The mean number of respiratory infections or episodes in each group was either not significantly different between groups, Cohen 2013a; Hatakka 2007a; Maldonado 2015; Tano 2002, or significantly lower among children in the probiotic group, Di Nardo 2014; Maldonado 2012.

Data for the number of children with respiratory infections in each group were pooled, showing that a smaller proportion of children in the probiotic group had respiratory infections (RR 0.74, 95% CI 0.62 to 0.88; P < 0.001; NNTB = 11; I^2 = 70%; moderate-certainty evidence; Analysis 1.7) (Corsello 2017; Di Pierro 2016; Hatakka 2001a; Hojsak 2010a; Hojsak 2016; Karpova 2015; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016).

Eleven trials reported on difference in GI infections, as follows: mean number of days with GI symptoms in each group (Hatakka 2001a; Stecksen-Blicks 2009); number of GI infections in each group (Di Nardo 2014; Maldonado 2012/Maldonado 2015); or number of children with GI infections (Cohen 2013a; Corsello 2017; Hojsak 2010a; Hojsak 2016; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016).

In one trial the mean number of days with GI symptoms did not differ significantly between groups (Hatakka 2001a), whilst in another trial, it was lower in the control group (1.1, SD 1.8) than in the probiotic group (1.7, SD 2.3) (intracluster coefficient 0.16) (Stecksen-Blicks 2009).

In one trial the number of GI infections in each group did not differ significantly between groups (Di Nardo 2014). In another trial there were significantly more GI events in the probiotic group than in the control group (incidence rate decrease 46%, P = 0.032) (Maldonado 2012), but not in the three-year follow-up (P = 0.947) (Maldonado 2015).

Data for studies that reported the number of children with GI infections in each group were pooled (Cohen 2013a; Corsello 2017; Hojsak 2010a; Hojsak 2016; Nocerino 2017; Rautava 2009; Taipale 2011/Taipale 2016), showing no difference between groups in the proportion of children with GI infections (RR 0.78, 95% CI 0.57 to 1.06; P = 0.11; I^2 = 61%; moderate-certainty evidence; Analysis 1.7).

Test for subgroup differences was not significant (P = 0.76).

9. Compliance with taking probiotics

Thirteen trials reported compliance with taking probiotics. Six trials reported on this outcome narratively, all stating that compliance was "good" or that the treatment was "well-received" (Corsello 2017; Di Pierro 2016; Maldonado 2012; Nocerino 2017; Stecksen-Blicks 2009; Taipale 2011). One trial reported on the percentage of capsules consumed (Hatakka 2007a), which was 96% in both groups. One trial reported the percentage of days during which consumption exceeded a prespecified amount (Hatakka 2001a), which was 60% in both groups. Five trials reported on the number of children complying or not complying with treatment (Cohen 2013a; Hojsak 2010a; Hojsak 2016; Marchisio 2015; Taipale 2016), permitting the pooling of data. Pooled data showed no significant difference between groups in compliance (RR 1.02, 95% CI 0.99 to 1.05; P = 0.21; I^2 = 0%; Analysis 1.8).

10. Quality of life measures

Hatakka 2001a reported on quality of life using the total symptom score (defined as a measure of the overall symptom burden, which consisted of the sum of all of the recorded symptoms ranging from 0 to 9). The difference between groups was not significant, with a mean unadjusted score of 34 in the probiotic group (95% CI 30 to 39) and 40 in the control group (95% CI 35 to 46), P = 0.10. Mean age-adjusted scores also did not differ significantly: the mean score was 36 for the probiotic group (95% CI 32 to 40) and 39 for the control group (95% CI 34 to 44), P = 0.36.

11. Difference in use of other treatments

Three trials reported on the difference between groups in the use of other treatments (Corsello 2017; Karpova 2015; Nocerino 2017).

Corsello 2017 reported a significantly lower use of antipyretics (P = 0.044) and corticosteroids (P = 0.027) in the probiotic group compared to the placebo group.

Nocerino 2017 reported a significantly lower use of antipyretics in one probiotic group (rice with *Lactobacillus paracasei* CBA L74, P = 0.001) and lower use of antipyretics in another probiotic group (milk with *Lactobacillus paracasei* CBA L74, P = 0.058) than in placebo. The study authors also reported a significantly lower use

of corticosteroids in one probiotic group (milk with *Lactobacillus paracasei*, P = 0.001) and lower use of corticosteroids in another probiotic group (rice with *Lactobacillus paracasei*, P = 0.07) than in placebo.

Karpova 2015 reported that 47% children in the probiotic group, compared to 93% in the control group, had prescriptions of intranasal corticosteroids (however, an inclusion criterion of this study was children with signs of chronic adenoiditis).

DISCUSSION

Summary of main results

This review suggests that probiotics prevent AOM, the primary outcome, by a clinically important amount. However, a subgroup analysis (not planned a priori) suggests that this effect was evident only in children who were not otitis-prone; the effect was not observed for otitis-prone children (as defined by studies themselves, and it is worth noting that the definition was not always clear and may have involved a subjective element). This is consistent with results from clinical trials of pneumococcal conjugate vaccines, which found a modest benefit for those already at low risk of AOM, but no protective effect for those with established recurrent disease, including otitis-prone children (Fortanier 2014). These findings may be due to clinical, pathological, and particularly immunological differences between children who are otitis-prone and those who are not otitis-prone (Pichichero 2016; Xu 2016).

Alternatively, there may be a methodological effect from increased bias, such as publication bias, of trials of children not prone to otitis media. Testing for publication bias by funnel plot does not support this, but statistical methods for determining publication bias are notoriously insensitive (Higgins 2011).

Another possibility is that any intervention effect is under-reported: diagnosis of AOM is notoriously difficult and frequently relies upon subjective clinical judgement (Pirozzo 2000). Some RCTs of interventions for AOM require special training in the diagnosis of AOM for participating clinicians, since overdiagnosis of AOM would decrease the intervention effect (Hoberman 2016). This is also problematic where allocation concealment and blinding of outcomes are incomplete, which even subconsciously risks influencing diagnostic behaviour, resulting in a potential misclassification bias.

However, efficacy was supported by some secondary outcomes: decreased infections other than AOM (for acute respiratory infections if not GI infections) and overall decreased antibiotic use (although unexpectedly for infections other than AOM, but not for AOM itself). Nevertheless, given the considerable variation in the probiotic strains trialled, their frequency, and duration of administration across studies, the optimal regimen is currently unclear. Further large and well-conducted RCTs, testing a range of probiotic strains and administration regimens (frequency, dose, duration), as well as collecting data on outcomes for which there is currently very limited evidence (e.g. severity of AOM, duration of AOM episodes, need for antibiotics, time off work for carer, hearing loss, referrals to specialists, and quality of life) may therefore help to resolve doubts about the real effectiveness of probiotics.

The pooled results found no consistent increase in adverse effects.

Overall completeness and applicability of evidence

We searched six distinct databases with no language restriction and searched trials registers, supplemented by forward- and backward-searching of cited works. However, we did not contact authors for additional research, nor did we handsearch conference proceedings, partly because there are no obvious conference candidates for this.

The volume of evidence varied considerably among the outcomes. There was sufficient evidence to perform meta-analyses for two of the primary outcomes (proportion of children with AOM and adverse events), but none of the included studies reported on the primary outcome severity of AOM.

The volume of evidence varied for the secondary outcomes. There was sufficient evidence to perform meta-analyses for four secondary outcomes (difference in the use of antibiotics, time off school for the child, difference in other infections, compliance with taking probiotics). Seven of the secondary outcomes were not meta-analysable. This was due to variability of reporting (difference in use of other treatments outcome) or paucity of evidence (two trials reported on the serous/secretory otitis media outcome; one trial reported on each of the following outcomes: median duration of AOM episodes, time off work for parent/carer, quality of life). No trials reported on referrals to specialist or difference in hearing loss between groups.

Quality of the evidence

We assessed the quality (certainty) of the evidence as moderate for most of the outcomes reported in the Summary of findings for the main comparison, including: proportion of children with AOM overall, proportion of children with AOM among children not prone to AOM, antibiotic use, and proportion of children with other infections. We assessed the quality of the evidence for one outcome - proportion of children with AOM among children who were prone to AOM - as high. No studies reported on the severity of AOM, therefore no quality of evidence rating was assigned. Risk of bias among the included studies was mostly related to allocation concealment, blinding of outcomes, and conflicts of interest and unclear role of funders in the trials.

Potential biases in the review process

Both clinical heterogeneity (especially from the disparate probiotic strains) and statistical heterogeneity confirmed our protocol-declared use of random-effects model analysis to avoid making inappropriate assumptions about the trials testing similar interventions. Heterogeneity was the principal reason for marking down the certainty of the evidence in the GRADE assessment (Summary of findings for the main comparison).

Biases could have arisen due to differences between the protocol and the systematic review (see the Differences between protocol and review section), in particular from: the broadening of the population (from children diagnosed with AOM to any children); omission of three of the prespecified subgroup analyses (one due to broadening of the population, two due to paucity of evidence); two subgroup analyses performed due to unanticipated availability of data (difference in the use of antibiotics, reduction in other infections). We did not perform sensitivity analysis (as only one included study was rated as having two domains at high risk of bias); the primary outcome was originally specified as incidence of

AOM, but was reported as proportion of children with AOM (due to variation in time points at which studies reported the outcome); and several outcomes had to be omitted, whilst others were added to the Summary of findings for the main comparison due to paucity or availability of evidence, respectively.

Agreements and disagreements with other studies or reviews

A previous systematic review found some evidence (in 4 out of 14 RCTs) for efficacy of probiotics as prophylaxis against the symptoms, but not the incidence, of acute respiratory tract infections in 3764 adults and children (Vouloumanou 2009). No meta-analysis was undertaken due to perceived heterogeneity of the interventions, populations, and diseases. A more recent systematic review and meta-analysis of 15 RCTs restricted to 5121 children also found evidence for a preventive reduction in the duration of acute respiratory tract infections (including AOM as a secondary outcome) in three of the trials, by about 0.75 of a day per year (Laursen 2018). (The authors were able to extract unpublished AOM-specific data from their own RCT, which was one of the trials included in the meta-analysis, Laursen 2017b).

It thus seems that our review is in accordance with this older literature.

AUTHORS' CONCLUSIONS

Implications for practice

A range of different probiotics may provide protection against acute otitis media (AOM) in children not prone to AOM, although it is possible that this effect is due to a bias not detected by our methods (such as publication bias, to account for the unexpected finding of better efficacy for non-otitis-prone children than otitis-prone ones, notwithstanding several biologically plausible explanations).

Many uncertainties remain about the use of probiotics to protect children from AOM: not just the concern that this is not a real effect (from bias distortion), but also about the nature of the intervention (can standard preparations of the probiotic be sourced for wholesale clinical practice), and a persistent concern that there may be insufficient data about safety from long-term observational trials (even though some trial data suggest they are safe in immunocompetent people) (Cohen 2018).

Uncertainties about the optimal strain, as well as the duration, frequency, and timing of probiotics administration, hamper the interpretation of results.

Implications for research

There is a clear need for more, and larger, well-conducted randomised controlled trials to test readily available probiotic preparations for AOM. Those randomised controlled trials should evaluate a variety of probiotic strains, as well as the duration, frequency, and timing of probiotic administration, as the optimal regimen is currently unclear. There is also either a paucity or an absence of evidence on the impact of probiotics on severity of AOM, median duration of AOM episodes, need for use of antibiotics, antimicrobial resistance, time off work for parent or carer, hearing loss, referrals to specialists, and quality of life (using validated tools). Uniform reporting of outcomes is crucial - for example reporting of antibiotic use varied significantly (e.g. as number of antibiotic courses, per cent of participants taking antibiotics, mean number of antibiotics prescriptions, days with antibiotic treatment, etc.), limiting its interpretive value. Finally, identifying children most likely to benefit from probiotics is an important research goal. This might include determining whether probiotics administered from shortly after birth protect high-risk (e.g. Indigenous) infants from AOM during the first years of life.

ACKNOWLEDGEMENTS

The authors would like to acknowledge and thank the authors of Crosby 2004, whose withdrawn protocol partly informed development of a re-developed protocol for this topic. Parts of the Background are based on a Cochrane Review by Venekamp 2015. One of the current authors (CDM) of this review is also an author on Crosby 2004 and Venekamp 2015. The Methods section of this protocol is based on a standard template developed by the Cochrane Airways Group and adapted by the Cochrane Acute Respiratory Infections Group. We wish to thank the following people for commenting on the draft of this protocol: Catherine Marshall, Jenny Negus, Roderick Venekamp, Tal Marom, Robert Ware, and Zulfiqar Bhutta. We wish to thank the following people for peer-reviewing the draft of this review: Roderick Venekamp, Daniel Merenstein, Rob Ware, Esther Martin, Janet Waddell, and An De Sutter. We also wish to thank Mark Jones for his statistical advice.

REFERENCES

References to studies included in this review

Cohen 2013a *{published data only}*

Cohen R, Martin E, de La Rocque F, Thollot F, Pecquet S, Werner A, et al. Probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children: a randomized, double-blind, placebo-controlled study. *Pediatric Infectious Disease Journal* 2013;**32**(8):810-4.

Corsello 2017 *{published data only}*

Corsello G, Carta M, Marinello R, Picca M, De Marco G, Micillo M, et al. Preventive effect of cow's milk fermented with Lactobacillus paracasei CBA L74 on common infectious diseases in children: a multicenter randomized controlled trial. *Nutrients* 2017;**9**:7. [DOI: 10.3390/nu9070669]

Di Nardo 2014 *{published data only}*

Di Nardo G, Oliva S, Menichella A, Pistelli R, De Biase RV, Patriarchi F, et al. Lactobacillus reuteri ATCC55730 in cystic fibrosis. *Journal of Pediatric Gastroenterology and Nutrition* 2014;**58**(1):81-6.

Di Pierro 2016 *{published data only}*

Di Pierro F, Colombo M, Giuliani MG, Danza ML, Basile I, Bollani T, et al. Effect of administration of Streptococcus salivarius K12 on the occurrence of streptococcal pharyngo-tonsillitis, scarlet fever and acute otitis media in 3 years old children. *European Review for Medical and Pharmacological Sciences* 2016;**20**(21):4601-6.

Hatakka 2001a *{published data only}*

Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, et al. Effect of long term consumption of probiotic milk on infections in children attending day care centres: double blind, randomised trial. *BMJ* 2001;**322**(7298):1327.

Hatakka 2007a *{published data only}*

Hatakka K, Blomgren K, Pohjavuori S, Kaijalainen T, Poussa T, Leinonen M, et al. Treatment of acute otitis media with probiotics in otitis-prone children - a double-blind, placebo-controlled randomised study. *Clinical Nutrition* 2007;**26**(3):314-21.

Hojsak 2010a *{published data only}*

Hojsak I, Snovak N, Abdovic S, Szajewska H, Misak Z, Kolacek S. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: a randomized, double-blind, placebo-controlled trial. *Clinical Nutrition* 2010;**29**(3):312-6.

Hojsak 2016 *{published data only}*

Hojsak I, Mocic Pavic A, Kos T, Dumancic J, Kolacek S. Bifidobacterium animalis subsp. lactis in prevention of common infections in healthy children attending day care centers - randomized, double blind, placebo-controlled study. *Clinical Nutrition* 2016;**35**(3):587-91.

Karpova 2015 *{published data only}*

Karpova EP, Karpycheva IE, Tulupov DA. Prophylaxis of chronic adenoiditis in the children. *Vestnik Otorinolaringologii* 2015;**80**(6):43-5.

Maldonado 2012 *{published data only}*

Maldonado J, Canabate F, Sempere L, Vela F, Sanchez AR, Narbona E, et al. Human milk probiotic Lactobacillus fermentum CECT5716 reduces the incidence of gastrointestinal and upper respiratory tract infections in infants. *Journal of Pediatric Gastroenterology and Nutrition* 2012;**54**(1):55-61.

Maldonado 2015 *{published data only}*

Maldonado LJA, Gil-Campos M, Maldonado J, López-Huertas E, Flores-Rojas K, Valero AD, et al. Long-term safety of early consumption of Lactobacillus fermentum CECT5716: a 3-year follow-up of a randomized controlled trial. *Pharmacological Research* 2015;**95-6**:12-9.

Marchisio 2015 *{published data only}*

Marchisio P, Santagati M, Scillato M, Baggi E, Fattizzo M, Rosazza C, et al. Streptococcus salivarius 24SMB administered by nasal spray for the prevention of acute otitis media in otitis-prone children. *European Journal of Clinical Microbiology & Infectious Diseases* 2015;**34**(12):2377-83.

Nocerino 2017 *{published data only}*

Nocerino R, Paparo L, Terrin G, Pezzella V, Amoroso A, Cosenza L, et al. Cow's milk and rice fermented with Lactobacillus paracasei CBA L74 prevent infectious diseases in children: a randomized controlled trial. *Clinical Nutrition* 2017;**36**(1):118-25.

Rautava 2009 *{published data only}*

Rautava S, Salminen S, Isolauri E. Specific probiotics in reducing the risk of acute infections in infancy - a randomised, double-blind, placebo-controlled study. *British Journal of Nutrition* 2009;**101**(11):1722-6.

Roos 2001a *{published data only}*

Roos K, Hakansson EG, Holm S. Effect of recolonisation with "interfering" alpha streptococci on recurrences of acute and secretory otitis media in children: randomised placebo controlled trial. *BMJ* 2001;**322**(7280):210-2.

Stecksen-Blicks 2009 *{published data only}*

Stecksen-Blicks C, Sjostrom I, Twetman S. Effect of long-term consumption of milk supplemented with probiotic lactobacilli and fluoride on dental caries and general health in preschool children: a cluster-randomized study. *Caries Research* 2009;**43**(5):374-81.

Taipale 2011 *{published data only}*

Taipale T, Pienihakkinen K, Isolauri E, Larsen C, Brockmann E, Alanen P, et al. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in infancy. *British Journal of Nutrition* 2011;**105**(3):409-16.

Taipale 2016 *{published data only}*

Taipale TJ, Pienihakkinen K, Isolauri E, Jokela JT, Soderling EM. Bifidobacterium animalis subsp. lactis BB-12 in reducing the risk of infections in early childhood. *Pediatric Research* 2016;**79**:65-9.

Tano 2002 *{published data only}*

Tano K, Hakansson EG, Holm SE, Hellstrom S. A nasal spray with alpha-haemolytic streptococci as long term prophylaxis against recurrent otitis media. *International Journal of Pediatric Otorhinolaryngology* 2002;**62**(1):17-23.

References to studies excluded from this review

Agustina 2012 *{published data only}*

Agustina R, Kok FJ, van de Rest O, Fahmida U, Firmansyah A, Lukito W, et al. Randomized trial of probiotics and calcium on diarrhea and respiratory tract infections in Indonesian children. *Pediatrics* 2012;**129**(5):e1155-64.

Ahanchian 2016 *{published data only}*

Ahanchian H, Jafari SA, Ansari E, Ganji T, Kiani MA, Khalesi M, et al. A multi-strain Synbiotic may reduce viral respiratory infections in asthmatic children: a randomized controlled trial. *Electron Physician* 2016;**8**(9):2833-9.

Arvola 1999 *{published data only}*

Arvola T, Laiho K, Torkkeli S, Mykkanen H, Salminen S, Maunula L, et al. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. *Pediatrics* 1999;**104**(5):e64.

Aryayev 2012 *{published data only}*

Aryayev ML, Bredeleva NK, Kononenko NA, Kukushin VN, Ignatenko AS, Ignatenko MI, et al. Experience of probiotic EcN-suspension use in preterm newborn infants for immunity improvement. First results of an ongoing study. *Monatsschrift fur Kinderheilkunde* 2012;**160**:76-7.

Auinger 2013 *{published data only}*

Auinger A, Riede L, Bothe G, Busch R, Gruenwald J. Yeast (1,3)-(1,6)-beta-glucan helps to maintain the body's defence against pathogens: a double-blind, randomized, placebo-controlled, multicentric study in healthy subjects. *European Journal of Nutrition* 2013;**52**(8):1913-8.

Bellomo 1980 *{published data only}*

Bellomo G, Mangiagle A, Nicastro L, Frigerio G. A controlled double-blind study of SF68 strain as a new biological preparation for the treatment of diarrhoea in pediatrics. Current Therapeutic Research 1980; Vol. 28:927-36.

Cáceres 2010 *{published data only}*

Cáceres P, Montes S, Vega N, Cruchet S, Brunser O, Gotteland M. Effects of Lactobacillus rhamnosus HN001 on acute respiratory infections and intestinal secretory IgA in children. *Journal of Pediatric Infectious Diseases* 2010;**5**(4):353-62.

Canani 2016 *{published data only}*

Canani RB, Corsello G, Nocerino R, Carta M, Marinello R, Picca M, et al. Effect of fermented milk with Lactobacillus paracasei CBA l74 on gastrointestinal and respiratory infections in children: multicenter randomized controlled trial. *Digestive and Liver Disease* 2016;**48**:E280-1.

Cazzola 2010 *{published data only}*

Cazzola M, Pham-Thi N, Kerihuel JC, Durand H, Bohbot S. Efficacy of a synbiotic supplementation in the prevention of common winter diseases in children: a randomized, double-blind, placebo-controlled pilot study. *Therapeutic Advances in Respiratory Disease* 2010;**4**(5):271-8.

Cobo 2006 *{published data only}*

Cobo Sanz JM, Mateos JA, Munoz Conejo A. Effect of Lactobacillus casei on the incidence of infectious conditions in children [Efecto de Lactobacillus casei sobre la incidencia de procesos infeeciosos en niñios/as]. *Nutricion Hospitalaria* 2006;**21**(4):547-51.

Collet 1993 *{published data only}*

Collet JP, Ducruet T, Kramer MS, Haggerty J, Floret D, Chomel JJ, et al. Stimulation of nonspecific immunity to reduce the risk of recurrent infections in children attending day-care centers. *Pediatric Infectious Disease Journal* 1993;**12**(8):648-52.

Corsello 2016 *{published data only}*

Corsello G, Nocerino R, Carta M, Mariniello R, Picca M, Marco G, et al. Effect of fermented milk with Lactobacillus paracasei CBA L74 on gastrointestinal and respiratory infections in children: multicenter randomized controlled trial. Digestive and Liver Disease 2016; Vol. 62:650.

Coulthard 2004 *{published data only}*

Coulthard MG, Mellis CM. A nasal spray with alpha-haemolytic streptococci as long term prophylaxis against recurrent otitis media. Medical Journal of Australia 2004; Vol. 181, issue 10:556-7.

Crawford 2015 *{published data only}*

Crawford P, Clauson E. Probiotics for the prevention of upper respiratory tract infections. *American Family Physician* 2015;**92**(7):573.

Dekker 2017 *{published data only}*

Dekker J, Xu L, Hong Q, Xiaoyang S. Bifidobacterium animalis subsp. lactis HN019 protects against respiratory tract infections in Chinese infants. Journal of Pediatric Gastroenterology and Nutrition 2017; Vol. 64:760.

Di Pierro 2012 *{published data only}*

Di Pierro F, Donato G, Fomia F, Adami T, Careddu D, Cassandro C, et al. Preliminary pediatric clinical evaluation of the oral probiotic Streptococcus salivarius K12 in preventing recurrent pharyngitis and/or tonsillitis caused by Streptococcus pyogenes and recurrent acute otitis media. *International Journal of General Medicine* 2012;**5**:991-6.

Garaiova 2015 *{published data only}*

Garaiova I, Muchova J, Nagyova Z, Wang D, Li JV, Orszaghova Z, et al. Probiotics and vitamin C for the prevention of respiratory tract infections in children attending preschool: a randomised controlled pilot study. *European Journal of Clinical Nutrition* 2015;**69**(3):373-9.

Gerasimov 2012 *{published data only}*

Gerasimov S, Cycura O. Role of probiotics in attenuation of acute respiratory tract infections in preschool and primary school children. *European Respiratory Journal* 2012;**40**:Abstract number: 1641.

Gerasimov 2016 *{published data only}*

Gerasimov SV, Ivantsiv VA, Bobryk LM, Tsitsura OO, Dedyshin LP, Guta NV, et al. Role of short-term use of L. acidophilus DDS-1 and B. lactis UABLA-12 in acute respiratory infections in children: a randomized controlled trial. *European Journal of Clinical Nutrition* 2016;**70**(4):463-9.

Gonchar 2015 *{published data only}*

Gonchar NV, Suvorov AN, Maryshev VP, Sorokina TM, Churkova TV, Kharit SM. Probiotics, nutritional status and resistance to respiratory infections in infants. *Eksperimentalnaija i Klinicheskaija Gastroenterologija* 2015;**1**(1):48-54.

Guillemard 2010 *{published data only}*

Guillemard E, Tanguy J, Flavigny A, de la Motte S, Schrezenmeir J. Effects of consumption of a fermented dairy product containing the probiotic Lactobacillus casei DN-114 001 on common respiratory and gastrointestinal infections in shift workers in a randomized controlled trial. *Journal of the American College of Nutrition* 2010;**29**(5):455-68.

Gutierrez-Castrellon 2014 *{published data only}*

Gutierrez-Castrellon P, Lopez-Velazquez G, Diaz-Garcia L, Jimenez-Gutierrez C, Mancilla-Ramirez J, Estevez-Jimenez J, et al. Diarrhea in preschool children and Lactobacillus reuteri: a randomized controlled trial. *Pediatrics* 2014;**133**(4):e904-9.

Hatakka 2001b *{published data only}*

Hatakka K, Savilahti E, Ponka A, Meurman JH, Poussa T, Nase L, et al. Magic bullet milk?. Forschende Komplementarmedizin und Klassische Naturheilkunde 2001; Vol. 8, issue 6:390.

He 2005 *{published data only}*

He M, Yang YX, Han H, Men JH, Bian LH, Wang GD. Effects of yogurt supplementation on the growth of preschool children in Beijing suburbs. *Biomedical and Environmental Sciences* 2005;**18**(3):192-7.

Hojsak 2009a *{published data only}*

Hojsak I, Abdovic S, Kolacek S. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children attending day care centres: a randomised, placebo-controlled, double-blind study. *Journal of Pediatric Gastroenterology and Nutrition* 2009;**48**:E71-2.

Hojsak 2009b *{published data only}*

Hojsak I, Abdovic S, Szajewska H, Kolacek S. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections: a randomised, placebo-controlled, double-blind study. *Journal of Pediatric Gastroenterology and Nutrition* 2009;**48**:E85-6.

Hojsak 2010b *{published data only}*

Hojsak I, Abdovic S, Szajewska H, Milosevic M, Krznaric Z, Kolacek S. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. *Pediatrics* 2010;**125**(5):e1171-7.

Hojsak 2015 *{published data only}*

Hojsak I, Tokic Pivac V, Mocic Pavic A, Pasini AM, Kolacek S. Bifidobacterium animalis subsp. lactis fails to prevent common infections in hospitalized children: a randomized, double-blind, placebo-controlled study. *American Journal of Clinical Nutrition* 2015;**101**(3):680-4.

ISCTRN 2004 *{published data only}*

ISRCTN53286030. A controlled trial of probiotics in the prevention of episodes of otitis media in general practice. http://www.isrctn.com/ISRCTN53286030 (date applied 30/09/2004).

Ito 2017 *{published data only}*

Ito M, Yumiko M, Ken K, Toshimitsu K, Haruo T, Noboru Y, et al. Randomized controlled trial of juzen-taiho-to in children with recurrent acute otitis media. *Auris Nasus Larynx* 2017;**44**(4):390-7.

Jespersen 2015 *{published data only}*

Jespersen L, Tarnow I, Eskesen D, Morberg CM, Michelsen B, Bugel S, et al. Effect of Lactobacillus paracasei subsp. paracasei, L. casei 431 on immune response to influenza vaccination and upper respiratory tract infections in healthy adult volunteers: a randomized, double-blind, placebo-controlled, parallel-group study. *American Journal of Clinical Nutrition* 2015;**101**(6):1188-96.

Kaplan 1968 *{published data only}*

Kaplan M, Fischgrund A, Dobrowolski B. Therapeutic effectiveness and clinical tolerance in children of a medication combining in the same preparation of a tetracycline base with lyophilized lactobacillus. *Semaine des Hospitaux* 1968;**44**(28):1889-93.

Kloster 2008 *{published data only}*

Kloster Smerud H, Ramstad Kleiveland C, Roll Mosland A, Grave G, Birkeland S-E. Effect of a probiotic milk product on gastrointestinal and respiratory infections in children attending day-care. Microbial Ecology in Health and Disease 2008; Vol. 20, issue 2:80-5.

Kukkonen 2008 *{published data only}*

Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, et al. Long-term safety and impact on infection rates of postnatal probiotic and prebiotic (synbiotic) treatment: randomized, double-blind, placebo-controlled trial. *Pediatrics* 2008;**122**(1):8-12.

Kumpu 2012 *{published data only}*

Kumpu M, Kekkonen RA, Kautiainen H, Jarvenpaa S, Kristo A, Huovinen P, et al. Milk containing probiotic Lactobacillus rhamnosus GG and respiratory illness in children: a randomized, double-blind, placebo-controlled trial. *European Journal of Clinical Nutrition* 2012;**66**(9):1020-3.

Kumpu 2013 *{published data only}*

Kumpu M, Lehtoranta L, Roivainen M, Ronkko E, Ziegler T, Soderlund-Venermo M, et al. The use of the probiotic Lactobacillus rhamnosus GG and viral findings in the nasopharynx of children attending day care. *Journal of Medical Virology* 2013;**85**(9):1632-8.

Laursen 2017a *{published data only}*

Laursen RP, Larnkjaer A, Ritz C, Hauger H, Michaelsen KF, Molgaard C. Probiotics and child care absence due to infections: a randomized controlled trial. *Pediatrics* 2017;**140**:2. [DOI: 10.1542/peds.2017-0735]

Lehtoranta 2012 *{published data only}*

Lehtoranta L, Soderlund-Venermo M, Nokso-Koivisto J, Toivola H, Blomgren K, Hatakka K, et al. Human bocavirus in the nasopharynx of otitis-prone children. *International Journal of Pediatric Otorhinolaryngology* 2012;**76**(2):206-11.

Li 2014 *{published data only}*

Li F, Jin X, Liu B, Zhuang W, Scalabrin D. Follow-up formula consumption in 3- to 4-year-olds and respiratory infections: an RCT. *Pediatrics* 2014;**133**(6):e1533-40.

Lin 2009 *{published data only}*

Lin JS, Chiu YH, Lin NT, Chu CH, Huang KC, Liao KW, et al. Different effects of probiotic species/strains on infections in preschool children: a double-blind, randomized, controlled study. *Vaccine* 2009;**27**(7):1073-9.

Luoto 2014 *{published data only}*

Luoto R, Ruuskanen O, Waris M, Kalliomaki M, Salminen S, Isolauri E. Prebiotic and probiotic supplementation prevents rhinovirus infections in preterm infants: a randomized, placebo-controlled trial. *Journal of Allergy and Clinical Immunology* 2014;**133**(2):405-13.

Maldonado 2010 *{published data only}*

Maldonado J, Lara-Villoslada F, Sierra S, Sempere L, Gomez M, Rodriguez JM, et al. Safety and tolerance of the human milk probiotic strain Lactobacillus salivarius CECT5713 in 6-month-old children. *Nutrition* 2010;**26**(11-2):1082-7.

Maldonado 2011 *{published data only}*

Maldonado J, Canabate F, Sempere L, Vela F, Sanchez AR, Narbona E, et al. A follow-on formula with the probiotic lactobacillus fermentum CECT5716 decreases the incidence of respiratory and gastrointestinal infections: a randomized controlled trial. Journal of Pediatric Gastroenterology and Nutrition 2011; Vol. 52:E63-4.

Marchisio 2010 *{published data only}*

Marchisio P, Esposito S, Bianchini S, Desantis C, Galeone C, Nazzari E, et al. Effectiveness of a propolis and zinc solution in preventing acute otitis media in children with a history of recurrent acute otitis media. *International Journal of Immunopathology and Pharmacology* 2010;**23**(2):567-75.

Marchisio 2016 *{published data only}*

Marchisio P, Esposito S, Principi N. The evidence for applying Streptococcus salivarius 24SMB by nasal spray for preventing recurrent acute otitis media. *European Journal of Clinical Microbiology and Infectious Diseases* 2016;**35**(11):1889-90.

Marchisio 2017 *{published data only}*

Marchisio P, Santagati M, Stefani S, Esposito S, Principi N. Topical intranasal bacteriotherapy: experience in acute otitis media. Italian Journal of Pediatrics 2017; Vol. 43, issue Suppl 1:no pagination.

Marogna 2014 *{published data only}*

Marogna M, Braidi C, Colombo C, Colombo F, Palumbo L, Compalati E. Sublingual allergoid immunotherapy for mites in the prevention of recurrent respiratory infections: a prospective real life study. Allergy 2014; Vol. 69:509.

Marseglia 2007 *{published data only}*

Marseglia GL, Tosca M, Cirillo I, Licari A, Leone M, Marseglia A, et al. Efficacy of Bacillus clausii spores in the prevention of recurrent respiratory infections in children: a pilot study. *Therapeutic and Clinical Risk Management* 2007;**3**(1):13-7.

Merenstein 2010 *{published data only}*

Merenstein D, Murphy M, Fokar A, Hernandez RK, Park H, Nsouli H, et al. Use of a fermented dairy probiotic drink containing Lactobacillus casei (DN-114 001) to decrease the rate of illness in kids: the DRINK study. A patient-oriented, double-blind, cluster-randomized, placebo-controlled, clinical trial. *European Journal of Clinical Nutrition* 2010;**64**(7):669-77.

Mizgier 2013 *{published data only}*

Mizgier Ml, Brignardello J, Morales P, Carvallo C, Cires MJ, Cruchet S, et al. Effect of the administration of a milk product containing a heat-treated probiotic and a prebiotic in preschool children. Annals of Nutrition and Metabolism 2013; Vol. 63, issue Suppl 1:1665.

Nocerino 2014 *{published data only}*

Nocerino R, Paparo L, Maddalena Y, Caprio S, Amato F, Pezzella V, et al. Novel dietary products derived by fermentation of cow milk and rice with Lactobacillus paracasei cbal74 prevent gastrointestinal and respiratory tract infections in young children: a prospective randomized controlled trial. Digestive and Liver Disease 2014; Vol. 46:e82.

Nocerino 2016 *{published data only}*

Nocerino R, Corsello G, Carta M, Marinello R, Picca M, De Marco G, et al. Effect of fermented milk with Lactobacillus paracasei CBA L74 on gastrointestinal and respiratory infections in children: multicenter randomized controlled trial. *Allergy* 2016;**71**:425.

Pitkaranta 2003 *{published data only}*

Pitkaranta A, Hatakka K, Blomgren K, Pohjavuori S, Korpela R. Probiotics in prevention of acute otitis media in otitis prone

children. Recent Advances In Otitis Media: Proceedings of the Eighth International Symposium; 2003 June 3-7;Marriott Harbor Beach Ft. Lauderdale, Florida. Pmph USA Ltd, 2003. [ISBN 13: 9781550092790]

Prodeus 2016 *{published data only}*

Prodeus A, Niborski V, Schrezenmeir J, Gorelov A, Shcherbina A, Rumyantsev A. Fermented milk consumption and common infections in children attending day-care centers: a randomized trial. *Journal of Pediatric Gastroenterology and Nutrition* 2016;**63**(5):534-43.

Puccio 2007 *{published data only}*

Puccio G, Cajozzo C, Meli F, Rochat F, Grathwohl D, Steenhout P. Clinical evaluation of a new starter formula for infants containing live Bifidobacterium longum BL999 and prebiotics. *Nutrition* 2007;**23**(1):1-8.

Ringel-Kulka 2015 *{published data only}*

Ringel-Kulka T, Kotch JB, Jensen ET, Savage E, Weber DJ. Randomized, double-blind, placebo-controlled study of synbiotic yogurt effect on the health of children. *Journal of Pediatrics* 2015;**166**(6):1475-81.e1-3.

Río 2002 *{published data only}*

Río ME, Zago BL, Garcia H, Winter L. The nutritional status change the effectiveness of a dietary supplement of lactic bacteria on the emerging of respiratory tract diseases in children [El estado nutricional modifica la efectividad de un suplemento dietario de bacterias lácticas sobre la aparición de patologías de vías respiratorias en niños]. *Archivos Latinoamericanos de Nutricion* 2002;**52**(1):29-34.

Rivero 2004 *{published data only}*

Rivero M, Roca A, Chifre R, Conde M, Rodriguez M, Santamaria A, et al. Effect of a new infant formula enriched with prebiotics, probiotics, nucleotides and LC-PUFAs on infants recovery after an infection. *Journal of Pediatric Gastroenterology and Nutrition* 2004;**39**(Suppl 1):S522.

Sazawal 2004 *{published data only}*

Sazawal S, Dhingra U, Sarkar A, Dhingra P, Deb S, Marwah D, et al. Efficacy of milk fortified with a probiotic Bifidobacterium lactis HN019 (DR-10 (TM)) and prebiotic galacto-oligosaccharides in prevention of morbidity - a community based double masked randomized trial. *PLOS ONE* 2004;**5**(8):e12164.

Sazawal 2010 *{published data only}*

Sazawal S, Dhingra U, Hiremath G, Sarkar A, Dhingra P, Dutta A, et al. Prebiotic and probiotic fortified milk in prevention of morbidities among children: community-based, randomized, double-blind, controlled trial. *PLOS One* 2010;**5**(8):e12164.

Schrezenmeir 2004 *{published data only}*

Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burow H, et al. Benefits of oral supplementation with and without synbiotics in young children with acute bacterial infections. *Clinical Pediatrics* 2004;**43**(3):239-49.

Skovbjerg 2009 *{published data only}*

Skovbjerg S, Roos K, Holm SE, Grahn Hakansson E, Nowrouzian F, Ivarsson M, et al. Spray bacteriotherapy decreases middle ear fluid in children with secretory otitis media. *Archives of Disease in Childhood* 2009;**94**(2):92-8.

Smith 2016 *{published data only}*

Smith TD, Watt H, Gunn L, Car J, Boyle RJ. Recommending oral probiotics to reduce winter antibiotic prescriptions in people with asthma: a pragmatic randomized controlled trial. *Annals of Family Medicine* 2016;**14**(5):422-30.

Stojkovic 2016 *{published data only}*

Stojkovic A, Simovic A, Bogdanovic Z, Bankovic D, Poskurica M. Clinical trial/experimental study (consort compliant): optimal time period to achieve the effects on synbiotic-controlled wheezing and respiratory infections in young children. *Serbian Archives of Medicine* 2016;**144**(1-2):38-45.

Timby 2015 *{published data only}*

Timby N, Hernell O, Vaarala O, Melin M, Lönnerdal B, Domellöf M. Infections in infants fed formula supplemented with bovine milk fat globule membranes. *Journal of Pediatric Gastroenterology and Nutrition* 2015;**60**(3):384-9.

Vlieger 2009 *{published data only}*

Vlieger AM, Robroch A, Van Buuren S, Kiers J, Rijkers G, Benninga MA, et al. Tolerance and safety of Lactobacillus paracasei ssp. paracasei in combination with Bifidobacterium animalis ssp. lactis in a prebiotic-containing infant formula: a randomised controlled trial. *British Journal of Nutrition* 2009;**102**(6):869-75.

Weizman 2006 *{published data only}*

Weizman Z, Alsheikh A. Safety and tolerance of a probiotic formula in early infancy comparing two probiotic agents: a pilot study. *Journal of the American College of Nutrition* 2006;**25**(5):415-9.

West 2008 *{published data only}*

West CE, Gothefors L, Granström M, Käyhty H, Hammarström MLKC, Hernell O. Effects of feeding probiotics during weaning on infections and antibody responses to diphtheria, tetanus and Hib vaccines. *Pediatric Allergy and Immunology* 2008;**19**(1):53-60.

Wright 2009 *{published data only}*

Wright A, Hawkins CH, Änggård EE, Harper DR. A controlled clinical trial of a therapeutic bacteriophage preparation in chronic otitis due to antibiotic-resistant Pseudomonas aeruginosa; a preliminary report of efficacy. *Clinical Otolaryngology* 2009;**34**(4):349-57.

References to ongoing studies

ACTRN12618000130268 *{published data only}*

ACTRN12618000130268. Effect of a probiotic on Otitis media (ear infections) and Upper Respiratory Tract Infections amongst 6-24 month old children [A randomised placebo controlled trial of the effect of BLIS probiotic, S. salivarius (K12) on Otitis

media (ear infections) and Upper Respiratory Tract Infections amongst 6-24 month old children, as measured by medical record events]. https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=374076 (date submitted 21/12/2017).

EUCTR2017-000820-83-FI *{published data only}*

EUCTR2017-000820-83-FI. An Open Label Extension Study of GBT440 Administered Orally to Patients with Sickle Cell Disease Who Have Participated in GBT440 Clinical Trials [An Open Label Extension Study of GBT440 Administered Orally to Patients with Sickle Cell Disease Who Have Participated in GBT440 Clinical Trials]. https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-004045-25/NL (date on which the record was first entered 2018-01-16).

ISRCTN53286030 *{published data only}*

ISRCTN53286030. A controlled trial of Probiotics in the prevention of episodes of otitis media in general practice [A controlled trial of Probiotics in the prevention of episodes of otitis media in general practice]. http://www.isrctn.com/ISRCTN53286030 (date applied 30/09/2004).

NCT01724203 *{published data only}*

NCT01724203. Effect of 12-week Probiotic Supplementation on Bacterial and Viral Infections in Infants Aged 6 to 12 Months [Effect of 12-week Probiotic Supplementation on Bacterial and Viral Infections in Infants Aged 6 to 12 Months: a Double-blind, Randomized, Placebo-controlled Study]. https://clinicaltrials.gov/ct2/show/NCT01724203 (first posted November 9, 2012).

NCT01909128 *{published data only}*

NCT01909128. Fermented Milk and Fermented Rice on the Appearance of Respiratory and Gastrointestinal Symptoms [Fermented Milk and Fermented Rice on the Appearance of Respiratory and Gastrointestinal Symptoms]. https://clinicaltrials.gov/ct2/show/NCT01909128 (first posted July 26, 2013).

NCT02221687 *{published data only}*

NCT02221687. The Combiotic-Study (GOLFIII) [Evaluation of the Efficacy and Safety of an Infant Formula Containing Synbiotics and Its Effects on the Incidence of Infectious Diseases in the Infant Gut : a Double-blind, Randomized, Controlled Interventional Study]. https://clinicaltrials.gov/ct2/show/NCT02221687 (first posted August 20, 2014).

NCT02802059 *{published data only}*

NCT02802059. E. Coli Nissle 1917 - Suspension for Infection Prophylaxis (RONi) [E. Coli Nissle 1917 - Suspension for Infection Prophylaxis]. https://clinicaltrials.gov/ct2/show/NCT02802059 (first posted June 16, 2016).

NCT03516409 *{published data only}*

NCT03516409. Bio-Kult Infantis® in AAD Prevention in Infants [Efficacy of a Synbiotic Product (Probiotics + Prebiotics) in the Prevention of Antibiotics-associated Diarrhoea (AAD) in Infants. A Multicenter, Double Blind, Parallel Group, Placebo Controlled, Randomized Study]. https://clinicaltrials.gov/ct2/show/NCT03516409 (first posted May 4, 2018).

NCT03614117 *{published data only}*

NCT03614117. Effect of a New Probiotic Strain on Recurrent Acute Otitis Media in Children (PROMAR) (PROMAR) [A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Effect of a Probiotic on Recurrent Acute Otitis Media (rAOM) in Children]. https://clinicaltrials.gov/ct2/show/NCT03614117 (first posted August 3, 2018).

Additional references

AAP 2013

American Academy of Pediatrics (AAP). Clinical practice guidelines: diagnosis and management of acute otitis media. *Pediatrics* 2013;**131**(3):e964-99.

Akkerman 2005

Akkerman AE, Kuyvenhoven MM, van der Wouden JC, Verhij TJM. Analysis of under- and overprescribing of antibiotics in acute otitis media in general practice. *Journal of Antimicrobial Chemotherapy* 2005;**56**:569-74.

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

Azarpazhooh 2016

Azarpazhooh A, Lawrence HP, Shah PS. Xylitol for preventing acute otitis media in children up to 12 years of age. *Cochrane Database of Systematic Reviews* 2016, Issue 8. [DOI: 10.1002/14651858.CD007095.pub3]

Cohen 2013b

Cohen R, Martin E, de la Rocque F, Thollot F, Pecquet S, Werner A, et al. Probiotics and prebiotics in preventing episodes of acute otitis media in high-risk children: a randomized double-blind, placebo-controlled study. *Pediatric Infectious Disease Journal* 2013;**32**(8):810-4.

Cohen 2018

Cohen PA. Probiotic safety - no guarantees. *JAMA Internal Medicine* 2018;**178**(12):1577-8. [DOI: 10.1001/jamainternmed.2018.5403]

Dagan 2016

Dagan R, Pelton S, Bakaletz L, Cohen R. Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease. *Lancet Infectious Diseases* 2016;**16**(4):480-92.

FAO-WHO 2006

Food, Agriculture Organization of the United Nations. World Health Organization (FAO-WHO). Probiotics in food: health and nutritional properties and guidelines for evaluation. www.fao.org/3/a-a0512e.pdf (accessed 7 March 2017).

Fortanier 2014

Fortanier AC, Venekamp RP, Boonacker CWB, Hak E, Schilder AGM, Sanders EAM, et al. Pneumococcal conjugate vaccines for preventing otitis media. *Cochrane*

Database of Systematic Reviews 2014, Issue 4. [DOI: 10.1002/14651858.CD001480.pub4]

Froom 2001

Froom J, Culpepper L, Green LA, de Melker RA, Grob P, Heeren T, et al. A cross-national study of acute otitis media: risk factors, severity, and treatment at initial visit. Report from the International Primary Care Network (IPCN) and the Ambulatory Sentinel Practice Network (ASPN). *Journal of the American Board of Family Practice* 2001;**14**:406-17.

GRADEpro GDT 2015 [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Hao 2015

Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database of Systematic Reviews* 2015, Issue 2. [DOI: 10.1002/14651858.CD006895.pub3]

Hatakka 2007b

Hatakka K, Blomgren K, Pohjavuori S, Kaijalainen T, Poussa T, Leinonen M, et al. Treatment of acute otitis media with probiotics in otitis-prone children - a double-blind, placebo-controlled randomised study. *Clinical Nutrition* 2007;**26**:314-21.

Hendley 2002

Hendley JO. Otitis media. *New England Journal of Medicine* 2002;**347**(15):1169-74.

Higgins 2011

Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hoberman 2016

Hoberman A, Paradise JL, Rockette HE, Kearney DH, Bhatnagar S, Shope TR, et al. Shortened antimicrobial treatment for acute otitis media in young children. *New England Journal of Medicine* 2016;**375**(25):2446-56.

Hozo 2005

Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**(13):1-10.

Jefferson 2018

Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database of Systematic Reviews* 2018, Issue 2. [DOI: 10.1002/14651858.CD004879.pub5]

Laursen 2017b

Laursen RP, Larnkjaer A, Ritz C, Hauger H, Michaelsen KF, Moelgaard C. Probiotics and child care absence due to infections: a randomised controlled trial. *Paediatrics* 2017;**140**(2):e20170735.

Laursen 2018

Laursen RP, Hojsak I. Probiotics for respiratory tract infections in children attending day care centers - a systematic review. *European Journal of Paediatrics* 2018;**177**(7):979-94. [DOI: 10.1007/s00431-018-3167-1]

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Marteau 2002

Marteau PR. Probiotics in clinical conditions. *Clinical Reviews in Allergy and Immunology* 2002;**22**(3):255-73.

McCullough 2017

McCullough AR, Pollack AJ, Plejdrup Hansen M, Glasziou PP, Looke DF, Britt HC, et al. Antibiotics for acute respiratory infections in general practice: comparison of prescribing rates with guideline recommendations. *Medical Journal of Australia* 2017;**207**(2):65-9.

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA Statement. *BMJ* 2009;**339**:2535.

Monasta 2012

Monasta L, Ronfani L, Marchetti F, Montico M, Vecchi Brumatti L, Bavcar A, et al. Burden of disease caused by otitis media: systematic review and global estimates. *PLOS ONE* 2012;**7**(4):e36226.

Niittynen 2012

Niittynen L, Pitkaranta A, Korpela R. Probiotics and otitis media in children. *International Journal of Otorhinolaryngology* 2012;**76**(4):465-70.

Norhayati 2017

Norhayati MN, Ho JJ, Azman MY. Influenza vaccines for preventing acute otitis media in infants and children. *Cochrane Database of Systematic Reviews* 2017, Issue 10. [DOI: 10.1002/14651858.CD010089.pub3]

O'Neill 2014

O'Neill J, Davies S, Rex J. Antimicrobial resistance: tackling a crisis for the health and wealth of nations. https://amr-review.org/sites/default/files/AMR%20Review%20Paper%20-%20Tackling%20a%20crisis%20for%20the%20health%20and%20wealth%20of%20nations_1.pdf (accessed 7 March 2017).

Pichichero 2016

Pichichero ME. Ten-year study of the stringently defined otitis-prone child in Rochester, NY. *Pediatric Infectious Disease Journal* 2016;**35**(9):1033-9.

Pirozzo 2000

Pirozzo S, Del Mar C. Chapter 27: Otitis media. Evidence Based Pediatrics and Child Health. London: BMJ Books, 2000.

RevMan 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roos 2001b

Roos K, Hakansson EG, Holm S. Effect of recolonisation with "interfering" alpha streptococci on recurrences of acute and secretory otitis media in children: randomised placebo controlled trial. *BMJ* 2001;**322**:1-4.

Rovers 2006

Rovers MM, Glasziou P, Appelman CL, Burke P, McCormick DP, Damoiseaux RA, et al. Antibiotics for acute otitis media: a meta-analysis with individual patient data. *Lancet* 2006;**368**(9545):1429-35.

Stool 1989

Stool SE, Field MJ. The impact of otitis media. *Pediatric Infectious Disease Journal* 1989;**8**(Suppl 1):11-4.

Tamir 2017

Tamir SO, Sibbald A, Rupa V, Marchisio P, Homoe P, Daniel SJ, et al. Gudelines for the treatment of acute otitis media: why are there worldwide differences?. *Current Otorhinolaryngology Reports* 2017;**5**(2):101-7.

Venekamp 2015

Venekamp RP, Sanders SL, Glasziou PP, Del Mar CB, Rovers MM. Antibiotics for acute otitis media in children. *Cochrane Database of Systematic Reviews* 2015, Issue 6. [DOI: 10.1002/14651858.CD000219.pub4]

Vouloumanou 2009

Vouloumanou EK, Makris GC, Karageorgopoulos DE, Falagas ME. Probiotics for the prevention of respiratory tract infections: a systematic review. *International Journal of Antimicrobial Agents* 2009;**34**(3):197.e1-10.

Wang 2016

Wang Y, Li X, Ge T, Xiao Y, Liao Y, Cui Y, et al. Probiotics for prevention and treatment of respiratory tract infections in children. *Medicine* 2016;**95**(31):e4509.

Xu 2016

Xu Q, Casey JR, Newman E, Pichichero ME. Otitis-prone children have immunologic deficiencies in naturally acquired nasopharyngeal mucosal antibody response after Streptococcus pneumoniae colonization. *Pediatric Infectious Disease Journal* 2016;**35**(1):54-60.

References to other published versions of this review

Crosby 2004

Crosby Z, Williamson I, Del Mar C, Little P. Probiotics for the prevention of acute otitis media in children. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD004978.pub2]

Scott 2018

Scott AM, Beller EM, Clark J, Roos K, Grimwood K, Little P, et al. Probiotics for preventing acute otitis media in children. *Cochrane Database of Systematic Reviews* 2018, Issue 1. [DOI: 10.1002/14651858.CD012941]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cohen 2013a

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: centralised randomisation without stratification was used with the Trial Balance programme on an Internet-based server to assign participants to groups Blinding: double-blind Duration: 12 months Exclusions postrandomisation: 236 randomised, 12 declined postrandomisation, 224 enrolled Losses to follow-up: Stage 1: probiotic group: 11 dropouts due to non-compliance with overall follow-up; control group: 11 dropouts due to non-compliance with overall follow-up Subsequently: probiotic group: 18 (8 due to non-compliance with treatment, 4 for personal reasons, 1 adenoidectomy scheduled, 1 adenoidectomy, 2 unknown, 5 adverse events); control group: 18 (9 non-compliance with treatment, 6 personal reasons, 1 adenoidectomy, 1 ichthyosis, 1 unknown, 1 tympanostomy)
Participants	Country: France Setting: children were enrolled by paediatricians

Cohen 2013a *(Continued)*

	Number of participants: 236 randomised (224 enrolled): 112 probiotic/prebiotic group, 112 control Age (mean +/- SD): 10.2 +/- 1.7 months Inclusion criteria: healthy infants, 7 to 13 months old, full-term birth, weight ≥ 6 kg at enrolment, AOM at the pre-inclusion visit treated with an antibiotic based on French guidelines and able to tolerate oral formula of 300 mL per day, at high risk of AOM (exposed to other children via day-care centre attendance or with ≥ 2 siblings), history of at least 1 episode of AOM before the current one Exclusion criteria: twins, children with underlying chronic disease, allergy to cow's milk protein, or participating in another clinical study
Interventions	Treatment group: NAN 3 formula with probiotic (*Streptococcus thermophilus* nCC 2496, *Streptococcus salivarius* dSM 13084, *Lactobacillus rhamnosus* lPr CgMCC 1.3724) and preB (raftilose/raftiline). Dose: *S thermophilus*: 1×10^7 CFU/g, *S salivarius*: 2.5×10^7 CFU/g, *L rhamnosus*: 1×10^7 CFU/g; aiming for 300 to 630 mL of formula consumed per day, for 12 months Comparator group: NAN 3 formula alone (placebo); aiming for 300 to 630 mL consumed per day, for 12 months
Outcomes	Primary outcome(s): incidence of AOM in each group in the 12 months Secondary outcome(s): URTI incidence, LRTI incidence, number of antibiotic treatment courses, number of children without a new episode of AOM, number of children with recurring AOM (3 episodes in 6 months or 4 episodes in 12 months)
Notes	Authors' COIs: 1 of the authors employed by study funder Funding: financial support provided by Nestle. Role of the funder in design, collection, analysis, interpretation of data, the writing of the manuscript, decision to submit the manuscript was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised randomisation without stratification was used with the Trial Balance programme to assign participants to groups.
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as "double blind".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons provided.
Selective reporting (reporting bias)	Unclear risk	All outcomes reported except incidence of URTIs (a secondary outcome).
Other bias	High risk	1 of the authors employed by study funder.

Cohen 2013a *(Continued)*

	Financial support provided by Nestle. Role of the funder in design, collection, analysis, interpretation of data, the writing of the manuscript, decision to submit the manuscript not reported. Other authors state no conflicts of interest or other funding to disclose.

Corsello 2017

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: randomisation was based on a list with consecutive numbers with an allocation ratio of 1:1 between groups Blinding: double-blind Duration: 90 days Exclusions postrandomisation: no child refused to participate after randomisation, and all of the children received the allocated intervention Losses to follow-up: probiotic 7 (reasons NR); placebo 13 (reasons NR)
Participants	Country: Italy Setting: children in the Italian public health system; recruited by paediatricians Number of participants: 146 randomised: 73 treatment group; 73 comparator group Age (mean +/- SD): 33 +/- 9 months Inclusion criteria: healthy children aged 12 to 48 months who were attending day care or preschool at least 5 days a week and who were regularly checked by the paediatricians involved in the trial were considered for the study, and were consecutively contacted during scheduled medical examinations at the paediatrician's office Exclusion criteria: age < 12 months or > 48 months, concomitant chronic infections, chronic systemic diseases, chronic inflammatory bowel diseases, autoimmune diseases, immunodeficiency, malignancy, metabolic diseases, chronic respiratory tract diseases including respiratory allergies and cystic fibrosis, malformations of gastrointestinal or urinary or respiratory tract, history of respiratory or gastrointestinal or urinary tract surgery, congenital cardiac defects, functional bowel disorders, suspected or challenge-proven food allergy, food intolerances, severe malnutrition (Z-score for weight-for-height < 3 SD scores), and use of antibiotics or pre/pro/synbiotics or immune-stimulating products in the 2 weeks before study enrolment. Siblings of participants enrolled in the study were not allowed to participate in the trial.
Interventions	Treatment group: 7 g cow's skim milk fermented with *Lactobacillus paracasei* (CBA L74), daily, for 90 days Comparator group: placebo (maltodextrins, with an energy content similar to that of the fermented milk), daily, for 90 days
Outcomes	Primary outcome(s): the rate of children experiencing at least 1 episode of common infectious disease Secondary outcome(s): total number of common infectious diseases, use of medications (antibiotics, antipyretics, corticosteroids), emergency department medical examinations, hospitalisations, days of work lost by the parents, days of school lost by the children, faecal levels of α- and β-defensins, cathelicidin (LL-37), and secretory immunoglobulin A (sIgA), adverse events
Notes	Authors' COIs: the authors declare they have no conflict of interest.

Corsello 2017 *(Continued)*

Funding: unrestricted grant from Heinz Italia (affiliate of Kraft Heinz Company). The funder had no influence on design, collection, analysis, interpretation of data, the writing of the manuscript, or the decision to submit the manuscript.

The trialled probiotic was manufactured by Heinz Italia SpA.

Note regarding meta-analysis: the study reports separate numbers for rhinitis, pharyngitis, laryngitis, tracheitis, otitis, for "common infectious diseases observed during the study period". For the 'difference in other infections' (ARIs) outcome, we reported the numbers for rhinitis only so as not to double count participants; when the numbers of all ARIs (rhinitis, pharyngitis, laryngitis, tracheitis, AOM) were added, they exceeded the number of children in the group, suggesting that at least some of the children had more than 1 ARI during the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study is described as randomised; baseline characteristics appear similar (Table 2).
Allocation concealment (selection bias)	Unclear risk	Not clearly reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The investigators were blinded to the treatment at all times. Intervention and control were in similar packaging, and products appeared the same.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A biostatistician blinded to the treatment allocation performed the statistical analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was reported for both arms, but no reasons provided. As attrition was less than 20% in both arms, we judged the risk of bias to be low.
Selective reporting (reporting bias)	Unclear risk	Emergency department visits (secondary outcome) not reported
Other bias	Low risk	Authors' COIs: the authors declare they have no conflict of interest. Funding: unrestricted grant from Heinz Italia (affiliate of Kraft Heinz Company). The funder had no influence on design, collection, analysis, interpretation of data, the writing of the manuscript, decision to submit the manuscript. The trialled probiotic was manufactured by Heinz Italia SpA.

Di Nardo 2014

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: allocation schedule was computer generated, using a random permuted blocks algorithm Blinding: double-blinded Duration: 6 months Exclusions postrandomisation: none

Di Nardo 2014 *(Continued)*

	Losses to follow-up: 1 discontinued in placebo group (consent withdrawn)
Participants	Country: Italy Setting: Dept of Paediatrics, University of Rome "La Sapienza" Number of participants: 61 randomised; 30 probiotic, 31 placebo Age (mean +/- SD): NR. Median: 17.5 years; range: 6 to 29 years Inclusion criteria: patients with cystic fibrosis, FEV1 > 70%; no inhaled or systemic corticosteroids; no anti-inflammatory drugs, antileukotrienes, and mast cell membrane stabilisers; and no serious organ involvement. (Although this study technically meets the exclusion criteria as it involves patients with cystic fibrosis, we have included this study because the study only included those with mild disease, who had limited respiratory impairment, and had not had a recent change in treatment.) Exclusion criteria: history of pulmonary exacerbation or upper respiratory infection in the previous 2 months; changes in medications in the last 2 months; history of haemoptysis in the last 2 months; and colonisation with *Burkholderia cepacia* or mycobacteria
Interventions	Treatment group: probiotic *Lactobacillus reuteri* ATCC55730; 5 drops per day (10^{10} CFU) for 6 months Comparator group: the placebo was packed in identical bottles, had the same colour, weight, smell, and taste of the probiotic formulation; 5 drops per day for 6 months
Outcomes	Primary outcome(s): number of episodes of pulmonary exacerbations; number and duration of hospital admissions made for pulmonary exacerbations; number of GI and upper respiratory tract infections Secondary outcome(s): change in qualitative and quantitative bacteria present in the sputum; FEV1; change in faecal calprotectin concentration; IL-8 and TNF-a levels in plasma and induced sputum
Notes	Authors' COIs: the authors report that they have no conflicts of interest Funding: intervention and placebo supplied by Italchimici (Pomezia, Italy), which had no role in the conception, design, conduct of the study, or in the analysis and interpretation of the data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised; no significant differences in baseline characteristics between the 2 groups
Allocation concealment (selection bias)	Low risk	Allocation schedule computer generated and fully concealed from doctors.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind; doctors and participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome measures of efficacy were recorded by investigators completely unaware of group assignment; unblinding procedures were performed after the study was completed and the statistical analysis carried out.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.

Di Nardo 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Intervention and placebo supplied by Italchimici (Pomezia, Italy), who had no role in the conception, design, conduct of the study, or in the analysis and interpretation of the data. The authors reported that they had no conflicts of interest.

Di Pierro 2016

Methods	Study design: 2-arm, controlled, randomised clinical study Method of randomisation: individuals were randomised into groups by toss of a coin Blinding: unblinded Duration: 180 days Exclusions postrandomisation: NR Losses to follow-up: the authors state that "none of the children were withdrawn from the study"
Participants	Country: Italy Setting: unclear Number of participants: 222 randomised; 111 treatment group, 111 placebo Age (mean +/- SD): treated group males: 36 +/- 3.2 months, females: 34 +/- 3 months; untreated group males: 35 +/- 3 months, females: 35 +/- 3.6 months Inclusion criteria: children around 3 years of age and soon to attend the first year of kindergarten; free of streptococcal disease, as established by a rapid throat swab test for group A streptococcus; none were clinically ill on enrolment Exclusion criteria: immunocompromised children; had undergone tonsillectomy or had an indication for adeno-tonsillectomy; had a history of rheumatic disorders, bronchospasm, and/or a diagnosis of asthma and/or allergy; a diagnosed respiratory or significant systemic disorder; were either undergoing current pharmacological therapies to prevent recurrent respiratory infections or presented with conditions that could favour the development of AOM, including severe atopy, acquired or congenital immunodeficiency, cleft palate, a chronically ruptured eardrum, craniofacial abnormalities or obstructive adenoids, sleep apnoea syndrome, or placement of tympanostomy tubes
Interventions	Treatment group: *Streptococcus salivarious* K12 (i.e. BLIS K12) probiotic strain, formulated as slowly dissolving oral tablets; containing no less than 1 billion CFU/tablet of *S salivarious* K12, 1 tablet/day, dissolved slowly in the mouth after brushing teeth/immediately before going to sleep, for 180 consecutive days Comparator group: untreated
Outcomes	Primary/secondary outcome(s): not specified, but the study states that it aimed to evaluate the following: (1) the onset of side effects or symptoms of toxicity while the product was being administered; (2) the efficacy of BLIS K12 in the prevention of *Streptococcus pyogenes* infections (pharyngo-tonsillitis and scarlet fever) during 6 months of treatment and a 3-month follow-up period; (3) the efficacy of BLIS K12 in reducing the occurrence of AOM
Notes	Authors' COIs: first author is the main formulator of the tested product and is involved in the Scientific Council of the company (Omeopiacenza) trading the tested product. The other authors report no conflicts of interest.

Di Pierro 2016 *(Continued)*

Funding: NR

Note regarding meta-analysis: this study only reports "pharyngo-tonsillitis" rather than ARIs generally (as other studies do in this analysis); we included these data in the analysis of the 'difference in other infections' outcome.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomised by tossed coin"; Table 1 suggests randomisation worked
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	High risk	Untreated group did not receive any treatment (i.e. unlikely patients/doctors blinded)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	"None of the children were withdrawn from the study"
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Authors' COIs: first author is the main formulator of the tested product and is involved in the Scientific Council of the company (Omeopiacenza) trading the tested product. The other authors report no conflicts of interest. Funding for the trial and the role of the funder: NR

Hatakka 2001a

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: computer-generated, blocked randomisation list; block size of 4, stratified according to age (< 3 years, and 3 years and over) and day-care centre (18 centres) Blinding: double-blinded Duration: 7 months Exclusions postrandomisation: discontinued before intervention: probiotic 14, placebo 9 Losses to follow-up: probiotic 30 (9 moving away from the area, 2 sickness, 8 other reasons, 11 unknown); placebo 28 (11 moving away from the area, 3 non-compliance, 3 sickness, 4 other reasons, 7 unknown)
Participants	Country: Finland Setting: day-care centres in Helsinki

Hatakka 2001a *(Continued)*

	Number of participants: randomised 594; probiotic 296, control 298 Age (mean, range): probiotic 4.6 (1.3 to 6.8) years, control 4.4 (1.3 to 6.7) years Inclusion criteria: healthy children aged 1 to 6 years, attending municipal day-care centres Exclusion criteria: children with allergy to cow's milk, lactose intolerance, severe food allergy, and other severe chronic diseases
Interventions	Treatment group: *Lactobacillus* milk (Gefilus, Valio, Riihimäki, Finland) containing 1% fat and 5 to 10 x 10^5 CFU/mL of strain *Lactobacillus rhamnosus* GG (ATCC 53103); 3 times a day, 5 days a week, for 7 months over the course of the winter Comparator group: control milk had the same composition as*Lactobacillus* milk, but did not contain *Lactobacillus*; 3 times a day, 5 days a week, for 7 months over the course of the winter
Outcomes	Primary outcome(s): the number of days with respiratory and gastrointestinal symptoms or days with any illness; absences from day-care centre because of illness; number of children with URTIs with complications (AOM and sinusitis) and LRTIs (acute bronchitis and pneumonia) as diagnosed by a doctor; antibiotic treatments during the 7-month intervention Secondary outcome(s): correlation between the amount of milk consumed and the number of days with symptoms; symptom score (measuring the overall burden of symptoms)
Notes	Authors' COIs: KH (first author) has been employed by Valio Research Centre (manufacturer of the trialled probiotic) for 2 of the past 5 years. MS and RK are employed by Valio Research Centre. ES has given 2 educational presentations on *Lactobacillus* GG for Valio, and TP has received consulting fees from Valio. Funding: Valio Research and Development, Helsinki, Finland. The University of Helsinki and the City of Helsinki participated in the funding by providing supervision and technical help. Role of the funders in design, collection, analysis, interpretation of data, the writing of the manuscript, decision to submit the manuscript not reported. ***Note regarding meta-analysis:*** for the 'difference in other infections (ARI)' outcome, we used data reporting "all infections together" (context suggests these were only respiratory infections) having first subtracted the number of children with AOM from this number.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated using a computer-generated randomisation list
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Day-care staff, parents, children, and investigators were unaware of which milk carton contained *Lactobacillus* until the intention-to-treat analysis was performed.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear whether outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported in both arms, with reasons.

Hatakka 2001a *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Authors' COIs: KH (first author) has been employed by Valio Research Centre (manufacturer of the trialled probiotic) for 2 of the past 5 years. MS and RK are employed by Valio Research Centre. ES has given 2 educational presentations on *Lactobacillus* GG for Valio, and TP has received consulting fees from Valio. Funding: Valio Research and Development, Helsinki, Finland. The University of Helsinki and the City of Helsinki participated in the funding by providing supervision and technical help. Role of the funders in design, collection, analysis, interpretation of data, the writing of the manuscript, decision to submit the manuscript not reported.

Hatakka 2007a

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: computer-generated blocked randomisation list drawn up by a statistician; block size of 4, stratified by gender, age (< 3 years old, ≥ 3 years old), and care type (home or small-group care or day care) Blinding: double-blinded Duration: 6 months Exclusions postrandomisation: none Losses to follow-up: probiotic 20 (4 sickness, 5 non-compliance, 5 personal reasons, 5 unknown, 1 adverse events); placebo 20 (3 sickness, 8 non-compliance, 0 personal reasons, 7 unknown, 2 tympanostomy)
Participants	Country: Finland Setting: NR Number of participants: 309 randomised; probiotic 155, placebo 154 Age (mean, range): probiotic group: 2.4 (0.8 to 6.0) years, placebo: 2.4 (0.9 to 5.6) years Inclusion criteria: at least 4 episodes of AOM during the preceding 12 months, or at least 3 episodes during the preceding 6 months Exclusion criteria: children on regular medication, with chronic illnesses, Down's syndrome, lip or palatal cleft, otitis media with effusion, or who were scheduled for tympanostomy or adenoidectomy during the study were excluded; those who had undergone tympanostomy or adenoidectomy during the preceding 6 months were also excluded unless they had suffered at least 3 episodes of AOM since the operations
Interventions	Treatment group: gelatin capsule containing a combination of probiotic bacteria (*Lactobacillus rhamnosus* GG, ATCC 53103; *L rhamnosus* LC 705; *Bifidobacterium breve* 99; *Propionibacterium freudenreichii* subsp. *shermanii*) 8 to 9 x 10^9 CFU/capsule of each strain, 1 capsule daily for 6 months Comparator group: capsule containing cellulose microcrystalline (identical looking to active intervention), 1 capsule daily for 6 months
Outcomes	Primary outcome(s): occurrence and duration of AOM episodes

Hatakka 2007a *(Continued)*

	Secondary outcome(s): frequency of pathogen carriage, the occurrence of recurrent URTIs, and the number of antimicrobial treatments
Notes	Authors' COIs: several authors employed or remunerated by manufacturer of the trialled probiotic Funding: manufacturer of trialled probiotic (Valio Ltd) and Helsinki University Hospital Research Fund funded the study. Role of the funders in design, collection, analysis, interpretation of data, the writing of the manuscript, decision to submit the manuscript not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated blocked randomisation list drawn by the statistician.
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators, parents, and children were all unaware of which treatment group each child was in until the statistical analysis was performed; capsules were delivered in coded containers.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, reasons provided.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Authors' COIs: several authors employed or remunerated by manufacturer of the trialled probiotic Funding: manufacturer of trialled probiotic (Valio Ltd) and Helsinki University Hospital Research Fund funded the study. Role of the funders in design, collection, analysis, interpretation of data, the writing of the manuscript, decision to submit the manuscript not reported.

Hojsak 2010a

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: randomisation performed with computer-generated numbers Blinding: double-blinded Duration: 3 months Exclusions postrandomisation: none Losses to follow-up: probiotic 12 (8 did not want to drink product anymore, 4 did not like the taste of product); placebo 15 (9 did not want to drink product anymore, 6 did not like the taste of product)

Hojsak 2010a *(Continued)*

Participants	Country: Croatia Setting: day-care centres in Zagreb Number of participants: 281 randomised; 139 probiotic, 142 placebo Age (mean, range): probiotic 51.9 (13 to 86) months; placebo 53.6 (13 to 83) months Inclusion criteria: children whose parents or legal guardians provided written informed consent and who did not meet any of the exclusion criteria Exclusion criteria: children with cow's milk allergy (probiotics were given in a fermented cow's milk product); those who were receiving probiotic or prebiotic products, or both prior to or at the time of enrolment; those who had a neoplasm, other chronic severe illness, or immunodeficiency; and children who disliked fermented milk products
Interventions	Treatment group: *Lactobacillus rhamnosus* strain GG (LGG strain from Valio) administered in 100 mL of a fermented milk product at a dose of 1 x 10^9 CFU, once daily during the 3-month intervention period (19 November 2007 to 20 February 2008) Comparator group: placebo was the same postpasteurised fermented milk product (100 mL) without LGG, once daily during the 3-month intervention period (19 November 2007 to 20 February 2008)
Outcomes	Primary outcome(s): (1) number of children with GI infections; (2) number of children with respiratory tract infections confirmed by physician Secondary outcome(s): (1) number of children with vomiting episodes; (2) number of children with diarrhoeal episodes; (3) number of GI infections lasting longer than 2 days; (4) number of children with URTI, including rhinitis, pharyngitis, sinusitis, otitis, and the common cold; (5) number of children with LRTIs, including pneumonia, bronchitis, and bronchiolitis; (6) number of respiratory tract infections lasting longer than 3 days; (7) total number of days with respiratory and GI symptoms; and (8) number of days absent from day-care centre due to infections
Notes	Authors' COIs: the authors report that before, during, or after the study, none of the authors received any funds for their work, which was exclusively voluntary, and the authors state that they have no conflict of interest Funding: probiotic and placebo supplied by Dukat Dairy Industry (dairy company in Croatia), who had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data ***Note regarding meta-analysis:*** this study reports the number of children with LRTIs and the number of children with URTIs separately. To report this outcome in the analysis of difference in other infections, we added the number of children with LRTI and URTI and subtracted from this number the number of children with AOM.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation procedure performed with computer-generated numbers.
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blind; neither research staff nor children were aware of the real nature of the product. Probiotic and placebo were packed in identical bottles, and were of the same colour, weight, smell, and taste.

Hojsak 2010a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unblinding procedure was performed after the study was completed and after the statistical analyses were finalised.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Authors' COIs: the authors report that before, during, or after the study, none of the authors received any funds for their work, which was exclusively voluntary, and the authors state that they have no conflict of interest Funding: probiotic and placebo supplied by Dukat Dairy Industry (dairy company in Croatia), who had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data

Hojsak 2016

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: used Random Allocation Software, in which every patient got a number and received the preparation successively; randomisation in blocks of 6 Blinding: double-blinded Duration: 90 days Exclusions postrandomisation: none Losses to follow-up: probiotic 5 (5 discontinued product use); placebo 7 (7 discontinued product use)
Participants	Country: Croatia Setting: day cares in Zagreb, Croatia Number of participants: 210 randomised; 104 probiotic, 106 placebo Age (mean, range): probiotic 4.49 (1.43 to 7.48) years; placebo 4.44 (1.44 to 6.79) years Inclusion criteria: children who attended day-care centres in 3 separate locations in the Zagreb area were eligible for the study, whose parents or legal guardians signed written informed consent, and who did not meet any of the exclusion criteria were included into the study Exclusion criteria: children receiving probiotic or prebiotic products, or both 2 weeks prior to or at the time of enrolment; those who had any severe chronic illness, including neoplasm and immunodeficiency
Interventions	Treatment group: a sachet containing 1 g of powder (maltodextrin with BB-12 at a dose of 10^9 CFU; the powder was mixed in about 20 mL of milk, water, cordial, or drinking yogurt or spread on a spoon of yogurt and consumed immediately thereafter, at home in the evening together with a meal. Once daily for 90 days (starting 23 January 2013). Comparator group: a sachet containing 1 g of powder (maltodextrin); the powder was mixed in about 20 mL of milk, water, cordial, or drinking yogurt or spread on a spoon of yogurt and consumed immediately thereafter, at home in the evening together with a meal. Once daily for 90 days (starting 23 January 2013).

Hojsak 2016 *(Continued)*

Outcomes	Primary outcome(s): number of children with common GI and respiratory infections. GI infections included diarrhoea, vomiting, both; ARIs included pharyngitis, otitis, common cold, pneumonia, bronchitis, and bronchiolitis diagnosed by physician. Secondary outcome(s): duration of symptoms of common infections (GI and ARIs); number of children with GI infections; number of children with ARIs; absence from day-care centre due to infections; use of antibiotics
Notes	Authors' COIs: the article states "none declared" Funding: Chr. Hansen, Denmark (manufacturer of the probiotic). The role of the funder in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported. ***Note regarding meta-analysis:*** for the 'difference in other infections' outcome, we have reported the numbers of children with ARIs but subtracted from those the number of children with AOM so as not to double count

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using Random Allocation Software
Allocation concealment (selection bias)	Low risk	"To ensure allocation concealment, an independent person prepared the randomisation schedule."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel, parents, and guardians were unaware of the group assignments. Products were of the same taste, colour, and smell, and were packed in identical sachets. The real nature of the product was not revealed to research staff and participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Statistical plan and complete statistical analysis was performed prior to unblinding, and all analyses were performed according to a written statistical analysis plan.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Authors' COIs: the article states "none declared" Funding: Chr. Hansen, Denmark (manufacturer of the probiotic). The role of the funder in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Karpova 2015

Methods	Study design: 2-arm, controlled, randomised clinical study Method of randomisation: the article states that it used "simple randomisation" (further details NR) Blinding: none (open) Duration: 30 days

Karpova 2015 *(Continued)*

	Exclusions postrandomisation: probiotics 15 (3 allergic reaction, 12 reasons not provided); control 19 (reasons not provided). 3 participants with allergic reaction were transferred to the control group and analysed as part of the control group. Losses to follow-up: none
Participants	Country: Russia Setting: children attending organised children's groups Number of participants: 250 children; 128 probiotic, 122 control; the study reports on 113 probiotic, 106 control Age: mean NR. Median NR. Range: 6 to 7 years old Inclusion criteria: children attending organised children's groups, aged 6 to 7 years, who had clinical signs of chronic adenoiditis Exclusion criteria: intolerance to flavouring components that make up the probiotic complex; presence of concomitant diseases that change the natural course of the disease, affect the result of therapy, and/or disrupt the possibility of subjective assessment of the symptoms of the disease (psychoneurological pathology, diabetes mellitus, blood diseases, oncological diseases, immunodeficiency conditions, gastrointestinal tract diseases, etc.)
Interventions	Treatment group: *Streptococccus salivarius* K12-based probiotic complex in combination with the nasal-douche, once daily at night for 30 days Comparator group: nasal-douche alone, once daily at night for 30 days
Outcomes	Primary/secondary outcome(s): unclear. The following outcomes listed: frequency of diagnosed adenoiditis, the need for topical anti-inflammatory therapy, complications of adenoiditis (AOM and acute rhinosinusitis), the need for systemic antibacterial drugs, side effects
Notes	Authors' COIs: NR Funding: NR. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported. ***Note regarding meta-analysis:*** for the analysis of difference in the use of antibiotics, we used the numbers reported in this study of children "prescribed antibiotics for AOM and acute rhinitis" (the numbers are reported collectively rather than individually by disease) in the 'use of antibiotics for AOM' subgroup rather than the 'use of antibiotics for any infection' subgroup as the former is a closer match. For the analysis of difference in other infections, we have reported the numbers for children with acute rhinosinusitis, as those are the only reported numbers (unlike other studies, which report 'ARIs' more collectively).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study states that it is randomised, but method not reported; no baseline characteristics provided to assess the result of randomisation.
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	NR

Karpova 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.
Selective reporting (reporting bias)	Unclear risk	Side effects are listed as one of the outcomes, but not reported.
Other bias	High risk	Authors' COIs: NR Funding: NR. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Maldonado 2012

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: computer-generated randomisation list Blinding: double-blinded Duration: 6 months Exclusions postrandomisation: probiotic 0; placebo 7 (7 did not receive the formula due to mistake in sending) Losses to follow-up: probiotic 7 (1 moved out of study area, 4 discontinued intervention/did not attend study visits, 2 excluded from analysis/incomplete data); placebo 13 (2 discontinued intervention, 6 discontinued intervention/did not attend study visits, 5 excluded from analysis/incomplete data)
Participants	Country: Spain Setting: paediatric departments of 3 hospitals Number of participants: 215 randomised; probiotic 117, control 98 Age (mean +/- SD): probiotic 6.5 +/- 1.2 months; control 6.5 +/- 1.3 months Inclusion criteria: healthy 6-month-old infants who were exclusively formula fed; live in proximity to the hospitals, child was delivered at the hospital and/or made regular visits to the paediatrician Exclusion criteria: GI disorders (history of chronic diarrhoea or constipation, gastro-oesophageal reflux), GI surgery, cow's milk protein allergy, metabolic disorders (diabetes, lactose intolerance), immunodeficiency, antibiotic prescription 1 week before inclusion, and previous use of formula containing prebiotics or probiotics
Interventions	Treatment group: standard powdered formula with nutritional composition in accordance with current European Union regulations, supplemented with (0.4 g/100 mL) galactooligosaccharide plus *Lactobacillus fermentum* CECT5716 (*L fermentum* Hereditum, Biosearch Life, Granada, Spain) at an average dose of 2 x 10^8 CFU/day. The amount of formula per day was paediatrician-prescribed; duration was 6 months. Comparator group: standard powdered formula with nutritional composition in accordance with current European Union regulations, supplemented with galactooligosaccharide only (0.4 g/100 mL). The amount of formula per day was paediatrician-prescribed; duration was 6 months.

Maldonado 2012 *(Continued)*

Outcomes	Primary outcome(s): incidence of infections (including GI, ARI, AOM, urinary, and other, less common infections) Secondary outcome(s): evolution of weight, length, and head circumference, fever episodes, antibiotic prescriptions, and concentrations of short-chain fatty acids (SCFAs), immunoglobulin (Ig) A, and microbiota composition in faeces; the incidence of recurrent (≥ 3 events) respiratory infections
Notes	Authors' COIs: the article states that "the authors report no conflict of interest" (NB: corresponding author lists affiliation with Puleva Food SL, which manufactured the formulas used in the trial) Funding: Puleva Food SL (manufacturer of the formulas; provided the formulas) The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list (SIGESMU, Madrid, Spain)
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double blind; "to ensure blinding, both formulas submitted to a sensorial test by an expert panel that finds both products to be identical"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data were analysed with STATA by a blinded statistician.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Authors' COIs: the article states that "the authors report no conflict of interest" (NB: corresponding author lists affiliation with Puleva Food SL, which manufactured the formulas used in the trial) Funding: Puleva Food SL (manufacturer of the formulas; provided the formulas). The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Maldonado 2015

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: computer-generated randomisation list Blinding: double-blinded

Maldonado 2015 *(Continued)*

	Duration: this is a 3-year follow-up of Maldonado 2012 (see above) Exclusions postrandomisation: 121 assessed for eligibility; 5 not located, 6 declined to participate; 110 included Losses to follow-up: probiotic 10 (did not attend medical visits); placebo 9 (did not attend medical visits)
Participants	Country: Spain Setting: children who completed the initial trial (Maldonado 2012) Number of participants: 110 included; probiotic 55, control 55 Age (mean +/- SD): probiotic: 3.02 +/- 0.1 years; control: 3.02 +/- 0.1 years Inclusion criteria: infants who had completed the previous trial (Maldonado 2012) Exclusion criteria: NR
Interventions	Treatment group (Maldonado 2012): standard powdered formula with nutritional composition in accordance with current European Union regulations, supplemented with (0.4 g/100 mL) galactooligosaccharide plus *Lactobacillus fermentum* CECT5716 (*L fermentum* Hereditum, Biosearch Life, Granada, Spain) at an average dose of 2 x 10^8 CFU/day. The amount of formula per day was paediatrician-prescribed; duration was 6 months. Comparator group (Maldonado 2012): standard powdered formula with nutritional composition in accordance with current European Union regulations, supplemented with galactooligosaccharide only (0.4 g/100 mL). The amount of formula per day was paediatrician-prescribed; duration was 6 months.
Outcomes	Primary outcome(s): anthropometric values including weight, length, and head circumference at 3 years of age Secondary outcome(s): incidence of non-acquired diseases (allergies and metabolic diseases), hospitalisations and surgical procedures, incidence of infections measured during the final year of the study
Notes	Authors' COIs: MG, JM, MVR, KF, and ELH acknowledge no conflict of interest of personal interest/gain in any company/organisation, or having received any financial support from any industry-related organisation in the preparation of this article. ADV, JF, and MO work for Biosearch, owner of the patent of *Lactobacillus fermentum* CECT5716. FLV works for Lactalis Puleva. JML is the recipient of a fellowship from the Fundación Universidad-Empresa (Universidad de Granada, Spain). Funding: the study was funded by HiPP GmbH & Co Vertrieb KG, Pfaffenhofen (Germany) and Lactalis Puleva, Granada (Spain). Study sponsors participated in the study design and the writing of the report.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised in the original study (Maldonado 2012)
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Original study described as double-blind; not clear if the 2-year follow-up was also blind for participants and personnel.

Maldonado 2015 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Authors' COIs: MG, JM, MVR, KF, and ELH acknowledge no conflict of interest of personal interest/gain in any company/organisation, or having received any financial support from any industry-related organisation in the preparation of this article. ADV, JF, and MO work for Biosearch, owner of the patent of *Lactobacillus fermentum* CECT5716. FLV works for Lactalis Puleva. JML is the recipient of a fellowship from the Fundación Universidad-Empresa (Universidad de Granada, Spain). Funding: the study was funded by HiPP GmbH & Co Vertrieb KG, Pfaffenhofen (Germany) and Lactalis Puleva, Granada (Spain). Study sponsors participated in the study design and the writing of the report.

Marchisio 2015

Methods	Study design: 2-arm, placebo-controlled, randomised controlled trial Method of randomisation: using a random number generator, in a 1:1 ratio Blinding: double-blinded Duration: 3 months Exclusions postrandomisation: none Losses to follow-up: probiotic 0; placebo 3 (refused to continue study after first treatment period)
Participants	Country: Italy Setting: Paediatric Highly Intensive Care Unit, Dept of Pathophysiology & Transplantation, University of Milan Number of participants: 100 randomised; 50 probiotic, 50 placebo Age (mean +/- SD): probiotic: 2.7 +/- 1.1 years; placebo: 3.1 +/- 1.2 years Inclusion criteria: children aged 1 to 5 years with histories of recurrent AOM (defined as at least 3 episodes in the preceding 6 months or at least 4 episodes in the preceding 12 months with the most recent episode within the previous 2 to 8 weeks) who were regularly followed up by the outpatient section of the Paediatric Highly Intensive Care Unit. The minimum number of episodes of AOM for inclusion in the otitis-prone group had to be diagnosed by pneumatic otoscopy performed by a trained investigator and documented by medical records, and at least 2 episodes had to be supported by tympanometric findings. At the time of enrolment, the children had to be free of AOM but could be experiencing otitis media with effusion. Exclusion criteria: all factors that could favour the development of AOM, including severe atopy, acquired or congenital immunodeficiency, cleft palate, a chronically ruptured eardrum, craniofacial abnormalities or obstructive adenoids, sleep apnoea syndrome, or the placement of tympanostomy tubes.

Marchisio 2015 *(Continued)*

Interventions	Treatment group: *Streptococcus salivarius* 24SMB preparation (suspension of *S salivarius* 24SMB consisting of a minimum of 100×10^9 CFU/mL in 5 mL of saline); delivered with a nasal spray that provided 5×10^9 CFU to each nostril; twice per day, 5 days each month for 3 consecutive months Comparator group: the placebo was based on saline with a colour and taste that were indistinguishable from the preparation containing *S salivarius*. The placebo was administered with the same nasal spray and provided the same saline dose; twice per day, 5 days each month for 3 consecutive months.
Outcomes	Primary/secondary outcome(s): not clearly identified. The article states: "Three types of outcome were considered, i.e., the total number of AOM episodes and the numbers of complicated and uncomplicated episodes."
Notes	Authors' COIs: the author(s) declare that they have no competing interests Funding: this study was supported by a grant obtained from DMG Italia S.r.l. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by "a random number generator"
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as double-blinded; paediatricians were blinded to treatment assignments. Both groups' sprays were labelled with randomisation codes.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Sprays' randomisation codes were revealed only to the staff of the data monitoring centre.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly identified as primary or secondary. Lists 3 outcomes (AOM episodes, complicated AOM episodes, uncomplicated episodes), all of which are reported, but the number of children treated with antibiotics is also reported in the results.
Other bias	High risk	Authors' COIs: the author(s) declare that they have no competing interests Funding: this study was supported by a grant obtained from DMG Italia S.r.l. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Nocerino 2017

Methods	Study design: 3-arm, placebo-controlled, randomised clinical study Method of randomisation: computer-generated randomisation list

Nocerino 2017 *(Continued)*

	Blinding: double-blinded Duration: 3 months Exclusions postrandomisation: probiotic in milk: 3 refused to participate after randomisation; probiotic in rice: 21 refused to participate after randomisation; placebo: 17 refused to participate after randomisation Losses to follow-up: probiotic in milk (4); probiotic in rice (5); placebo (5)
Participants	Country: Italy Setting: family paediatricians in the Italian Public Health System Number of participants: randomised 432: probiotic in milk: 144; probiotic in rice 144; placebo 144 Age (mean +/- SD): probiotic in milk: 32 +/- 30 months; probiotic in rice: 31 +/- 11 months; placebo: 34 +/- 9 months Inclusion criteria: consecutive healthy children (12 to 48 months of age) attending day care or preschool at least 5 days a week Exclusion criteria: age ≤ 12 months or ≥ 48 months, concomitant chronic systemic diseases, congenital cardiac defects, gastrointestinal or urinary or respiratory tract surgery, active tuberculosis, autoimmune diseases, immunodeficiency, chronic inflammatory bowel diseases, cystic fibrosis, metabolic diseases, history of suspected or challenge-proved food allergy, lactose intolerance, malignancy, chronic pulmonary diseases, malformations of gastrointestinal or urinary or respiratory tract, severe malnutrition (Z score for weight-for-height < 3 SD scores); use of pre/pro/synbiotics, antibiotics, or immune-stimulating products in the 2 weeks before study enrolment
Interventions	Probiotic in milk: cow's milk fermented with *Lactobacillus paracasei* CBA L74. 7 g/day of study product diluted in maximum 150 mL of cow's milk or water. Daily for 3 months during the winter season. Probiotic in rice: rice fermented with *L paracasei* CBA L74. 7 g/day of study product diluted in maximum 150 mL of cow's milk or water. Daily for 3 months during the winter season. Comparator group: placebo consisting of maltodextrins with similar energy content of fermented milk and rice products. 7 g/day of study product diluted in maximum 150 mL of cow's milk or water. Daily for 3 months during the winter season.
Outcomes	Primary outcome(s): the proportion of children experiencing at least 1 episode of common infectious disease Secondary outcome(s): proportion of children with recurrent common infectious diseases (i.e. 3 episodes), total number of common infectious diseases, use of medications (antipyretics, antibiotics, or corticosteroids), emergency department visits, paediatric visits, hospitalisations
Notes	Authors' COIs: the authors state that they have no financial relationships relevant to this article to disclose. The authors have no conflicts of interest that are directly relevant to the content of this paper. Funding: this work was supported in part by the Italian Ministry of Health Grant PE-2011-02348447, and by an unrestricted grant from Heinz Italia SpA, Latina, Italy, an affiliate of H.J. Heinz Company, Pittsburgh, PA, USA, devoted to the Department of Translational Medical Science of the University of Naples "Federico II". However, neither the Italian Ministry of Health nor Heinz Italia SpA, Latina, Italy, an affiliate of H.J. Heinz Company, Pittsburgh, PA, USA had any influence on: 1) the study design, 2) the collection, analysis, and interpretation of data; 3) the writing of the manuscript; and 4) the decision to submit the manuscript for publication.

Risk of bias

Bias	Authors' judgement	Support for judgement

Nocerino 2017 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomised according to a computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	The paediatricians assigned each child to the next available number on entry into the trial.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Investigators were blinded to the treatment at all times. Paediatricians, parents, and children were not aware of the dietary treatment assigned.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Statistical analysis was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for all 3 arms, with reasons.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Authors' COIs: the authors state that they have no financial relationships relevant to this article to disclose. The authors have no conflicts of interest that are directly relevant to the content of this paper. Funding: this work was supported in part by the Italian Ministry of Health Grant PE-2011-02348447, and by an unrestricted grant from Heinz Italia SpA, Latina, Italy, an affiliate of H.J. Heinz Company, Pittsburgh, PA, USA, devoted to the Department of Translational Medical Science of the University of Naples "Federico II". However, neither the Italian Ministry of Health nor Heinz Italia SpA, Latina, Italy, an affiliate of H.J. Heinz Company, Pittsburgh, PA, USA had any influence on: 1) the study design, 2) the collection, analysis, and interpretation of data; 3) the writing of the manuscript; and 4) the decision to submit the manuscript for publication.

Rautava 2009

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: block randomisation with individual codes Blinding: double-blinded Duration: 10 to 12 months (infants < 2 months old were recruited and followed until they were 12 months old) Exclusions postrandomisation: none Losses to follow-up: probiotic 2; placebo 1 Non-adherence to protocol: probiotic 9 (4 discontinued, 2 GI complaints, 2 inconvenience of powdered formula, 1 arduousness of study); placebo 4 (2 discontinued, 1 GI complaints, 1 arduousness of study)
Participants	Country: Finland Setting: NR Number of participants: 81 randomised; probiotics 38, placebo 43

Rautava 2009 *(Continued)*

	Age (mean age in days at start of intervention): probiotics 38 (6 to 65), placebo 35 (2 to 59) Inclusion criteria: need for infant formula before the age of 2 months Exclusion criteria: infants with chronic disease
Interventions	Treatment group: 1 x 10^{10} CFU of both *Lactobacillus rhamnosus* (*Lactobacillus* GG, American type culture collection 53103; Valio Ltd, Helsinki, Finland) and *Bifidobacterium lactis* Bb-12 (Chr. Hansen A/S, Hoersholm, Denmark) in capsule, the contents of which were supplemented to infant formula given at 1 feeding. Once daily, until the age of 12 months. Comparator group: placebo capsule (microcrystalline cellulose) in capsule, the contents of which were supplemented to infant formula given at 1 feeding. Once daily, until the age of 12 months.
Outcomes	Primary outcome(s): incidence of early ARIs, doctor-diagnosed AOM, GIs occurring before the age of 7 months Secondary outcome(s): incidence of recurrent (3+) respective infections during the first year of life
Notes	Authors' COIs: NR Funding: *Lactobacillus* GG was acquired without cost from Valio Ltd, and Chr. Hansen A/S provided *B lactis* Bb-12 and manufactured the probiotic and placebo capsules without cost. The infant formula was provided without cost by Mead Johnson Nutrition. The study was funded by the Microbes and Man research programme, the Academy of Finland, and the Bristol-Myer Squibb Mead Johnson Foundation Unrestricted Research Grant. The funding sources had no involvement in study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by block randomisation with individual codes
Allocation concealment (selection bias)	Unclear risk	The random allocation was generated independently from the investigators by the manufacturer of the capsules (Chr. Hansen A/S).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study was double-blind; the code was opened after all the infants had completed the study and data had been edited.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clear who performed the assessment or whether or not they were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	*Lactobacillus* GG was acquired without cost from Valio Ltd, and Chr. Hansen A/S provided *B lactis* Bb-12 and manufactured the probiotic and placebo capsules without cost. The infant formula was provided without cost by Mead Johnson Nutrition. The study was funded by the Microbes and Man research programme, the Academy of Finland, and the Bristol-Myer Squibb Mead John-

Rautava 2009 *(Continued)*

	son Foundation Unrestricted Research Grant. The funding sources had no involvement in study design, collection, analysis, and interpretation of data, writing of the report, or the decision to submit the paper for publication. Author COIs not reported.

Roos 2001a

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: randomisation was undertaken by a technician with no access to information on the participants or doctors; no further details provided Blinding: double-blinded Duration: 3 months Exclusions postrandomisation: not clear, of 132 children included, 108 (82%) were eligible for analysis of efficacy (53 in the probiotic group and 55 in the placebo group) and 126 (95%) for analysis of adverse events Losses to follow-up: not reported by assigned group; main reasons for not being eligible for the efficacy analysis were withdrawal from the study or refusal to start spray treatment (8 children), inadequate handling of spray (4), and antibiotic treatment being received for reasons other than AOM (3). The other 5 participants were either lost to follow-up (2), allergic to penicillin (1), or it was not possible to determine whether a recurrence had occurred because they were treated by another doctor during the study (2).
Participants	Country: Sweden Setting: ENT specialists at Lundby Hospital Number of participants: 130 randomised; 108 eligible for efficacy analysis (53 in probiotic group, 55 in placebo group) Age (mean, range): 23 months (6 months to 6 years) Inclusion criteria: had had recurrent AOM and who had been either referred by their general practitioner or a paediatrician to the open care unit of the ear, nose, and throat department at Lundby Hospital or were directly seeking medical advice for ear pain; had had at least 2 episodes of AOM during the past 6 months or 5 episodes during the past year; at the next occurrence of ear pain the children were examined, and those with a red or pale, bulging, thickened tympanic membrane were included in the study Exclusion criteria: penicillin allergy, serious underlying disease, immunological deficiency, a valvular heart defect, major lesions in the mouth or nose, a grommet in the ear, or chronic otitis media
Interventions	Treatment group: streptococcal spray (2 strains of *Streptococcus sanguis*, 2 strains of *S mitis*, 1 strain of *S oralis*), freeze-dried in skim milk, reconstituted in 0.9% sodium chloride immediately prior to use; corresponding to a suspension of 5 x 10^8 CFU/mL. Children with no recurrences during the last month received phenoxymethylpenicillin (n = 22), and those with a recurrence within 1 month received amoxicillin-clavulanic acid (n = 86), both twice a day for 10 days. Streptococcal spray was then sprayed into the nose for 10 days (3 puffs into each nostril, twice daily). At day 60, the same spray was administered for another 10 days (3 puffs into each nostril, twice daily). Comparator group: placebo comprised of skim milk powder (with the same texture and colour as the spray). Children with no recurrences during the last month received phenoxymethylpenicillin (n = 22), and those with recurrence within 1 month received amoxicillin-clavulanic acid (n = 86), both twice a day for 10 days. Placebo spray was then sprayed into the nose for 10 days (3 puffs into each nostril, twice daily). At day 60, the same spray was administered for another 10 days (3 puffs into each nostril, twice daily).

Roos 2001a *(Continued)*

Outcomes	Primary outcome(s): recurrence of AOM during follow-up; normal tympanic membrane at the last valid visit Secondary outcome(s): unclear
Notes	Authors' COIs: the authors of this study have been co-operating for over 15 years in the study of recurrent infections in the upper respiratory tract, and the present study is a continuation of earlier studies on bacterial interference done by the authors. The Medical Products Agency in Uppsala approved the design and suggested minor changes. Funding: Swedish National Board for Industrial and Technical Development; Teknikbro Foundation; Samariten Foundation. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by a technician with no access to information on participants or doctors.
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study described as "double blind"; placebo powder was the same texture and colour as the intervention.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons provided.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Authors' COIs: the authors of this study have been co-operating for over 15 years in the study of recurrent infections in the upper respiratory tract, and the present study is a continuation of earlier studies on bacterial interference done by the authors. The Medical Products Agency in Uppsala approved the design and suggested minor changes. Funding: Swedish National Board for Industrial and Technical Development; Teknikbro Foundation; Samariten Foundation. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Stecksen-Blicks 2009

Methods	Study design: 2-arm, placebo-controlled, cluster-randomised clinical study Method of randomisation: clusters (different day cares) were randomly allocated to the intervention or control regimen by a staff member at the local dairy by coin toss

Stecksen-Blicks 2009 *(Continued)*

	Blinding: double-blinded Duration: 21 months Exclusions postrandomisation: none Losses to follow-up: Before 12 months: probiotic 23 (22 children moved to school after 3 months, 1 child changed unit); control 39 (36 children moved to school after 3 months; 3 milk intolerance) After 12 months but before 21 months: probiotic 26 (moved to school after 15 months); control 31 (moved to school after 15 months)
Participants	Country: Sweden Setting: day-care centres Number of participants: randomised 27 units (n = 248); probiotic 16 units (n = 133), control 11 units (n = 115) Age (mean +/- SD at baseline): probiotic 42.9 +/- 16.5 months; control 42.4 +/- 13.8 months Inclusion criteria: children 1 to 5 years old, from 14 day-care centres located in Nordmaling and Hörnefors Exclusion criteria: severe chronic diseases, milk intolerance, or with a fluoride concentration in piped drinking water exceeding 0.5 mg/L were excluded
Interventions	Treatment group: 150 mL medium-fat milk (1.5%) at lunch; the milk was prepared by the day-care staff by adding 1 colour-coded capsule (10 mL) to each litre of milk. The capsules were kept frozen and contained fluoride and probiotic bacteria in skim milk to give a final concentration of 2.5 mg/L fluoride and 10^7 CFU/mL *Lactobacillus rhamnosus* LB21 in the intervention group. The milk was served only on weekdays and not during weekends, holidays, or vacation periods; once daily for 21 months. Comparator group: children were served 150 mL medium-fat milk (1.5%) at lunch. Before serving, the milk was prepared by the day-care staff by adding 1 colour-coded capsule (10 mL) to each litre of milk. The capsules in the control group contained only skimmed milk and were identical in appearance except in colour code. The intervention milk was served only on weekdays and not during weekends, holidays, or vacation periods; once daily for 21 months.
Outcomes	Primary outcome(s): caries increment Secondary outcome(s): "measures of general health"
Notes	Authors' COIs: NR Funding: the probiotic strain was provided by Essum AB, Umeå, Sweden. The fluoride solution was prepared at the university biochemical laboratory, and the capsules were produced at the local dairy (Norrmejerier, Umeå, Sweden). The study was supported financially by the County Council of Västerbotten (TUA) and the Borrow Foundation, UK. Norrmejerier Ekonomisk Förening, Umeå, Sweden supported the study by preparation and distribution of the milk. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Day-care units were randomly allocated by a staff member at the local dairy by means of coin tossing.

Stecksen-Blicks 2009 *(Continued)*

Allocation concealment (selection bias)	Low risk	The units were referred to as blue or yellow units in order to conceal their allocation. The code was kept by an independent monitor and was not unveiled until all data were computerised.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither the researchers nor the clinicians, personnel, or families at the day-care centres knew whether the children had received control or intervention milk during the course of the study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons provided.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Authors' COIs: NR Funding: the probiotic strain was provided by Essum AB, Umeå, Sweden. The fluoride solution was prepared at the university biochemical laboratory, and the capsules were produced at the local dairy (Norrmejerier, Umeå, Sweden). The study was supported financially by the County Council of Västerbotten (TUA) and the Borrow Foundation, UK. Norrmejerier Ekonomisk Förening, Umeå, Sweden supported the study by preparation and distribution of the milk. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Taipale 2011

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: computer-generated randomisation list; blocks of 3 Blinding: double-blinded Duration: approximately 7 months (from age 1 to 2 months to 8 months) Exclusions postrandomisation: none Losses to follow-up: probiotic group: 17 did not receive tablet; control group: 17 did not receive tablet Non-adherence to protocol: probiotic group 4 (2 GI complaints, 2 arduousness of study); control group 2 (1 atopic eczema, 1 arduousness of study)
Participants	Country: Finland Setting: recruited via pamphlets at well-baby clinic Number of participants: randomised 109; probiotic 55, control 54 Age: not reported, but participants were "1 month old infants" Inclusion criteria: (1) the child was healthy, (2) the parents were willing to use the novel slow-release pacifier, and (3) the child started receiving the tablet before the age of 2 months. In cases where the

Taipale 2011 *(Continued)*

	child did not start using the pacifier but the parents were motivated to remain in the study, they were offered the possibility of delivering the crushed tablet to the child using a spoon. Exclusion criteria: NR
Interventions	Treatment group: the probiotic bacterium used was BB-12 (DSM 15 954; Chr. Hansen A/S, Hoersholm, Denmark). 2 probiotic tablets per day via a novel slow-release pacifier (pacifier contains a pouch in which the tablet is inserted); each tablet contained 5 billion CFU of BB-12. Until 6 to 8 months of age, the children received the tablet via a small pacifier, thereafter via a larger pacifier. The tablet in the small pacifier contained 100 mg xylitol; the tablet in the larger pacifier contained 300 mg xylitol, both in addition to BB-12. Duration: from age 1 to 2 months to 8 months. Comparator group: the control tablets contained xylitol alone. Duration: from age 1 to 2 months to 8 months.
Outcomes	Primary outcome(s): reported cumulative incidence of ARIs and doctor-diagnosed AOM occurring before the age of 8 months Secondary outcome(s): successful intestinal passage of BB-12 (*Bifidobacterium animalis* subsp. *lactis*)
Notes	Authors' COIs: 1 author (TT) states "no conflict of interest". 1 author (CL) lists an affiliation with Chr. Hansen (which donated the BB-12 probiotics) in the author affiliations, but this is not noted in the COI. No information on COIs of the remaining authors. Funding: TT had no conflicts of interest. He was supported by personal grants from the Emil Aaltonen and Sohlberg Foundations, Finnish Dental Society Apollonia, and the Finnish Dental Association. The funding sources had no involvement in study design, interpretation of data, writing of the paper, or the decision to submit the paper for publication. Chr. Hansen A/S (Hoersholm, Denmark) donated the BB-12 for the probiotic tablets and helped in carrying out the faecal analysis of BB-12. The tablets were manufactured by Oy Karl Fazer Ab (Vantaa, Finland). The pacifiers were manufactured by Mekalasi Oy (Konnevesi, Finland). Neither Hansen, Fazer, or Mekalasi provided financial support for this clinical study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study described as randomised; baseline characteristics appear similar between groups.
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All of the study personnel and participants were blinded to the treatment assignment for the duration of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only 1 of the authors (ES) had the code, but this author did not participate in producing or analysing the data at any stage of the trial and had no contact with the study participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons provided.
Selective reporting (reporting bias)	Low risk	All outcomes reported.

Taipale 2011 *(Continued)*

Other bias	High risk	TT had no conflicts of interest. He was supported by personal grants from the Emil Aaltonen and Sohlberg Foundations, Finnish Dental Society Apollonia, and the Finnish Dental Association. The funding sources had no involvement in study design, interpretation of data, writing of the paper, or the decision to submit the paper for publication. Chr. Hansen A/S (Hoersholm, Denmark) donated the BB-12 for the probiotic tablets and helped in carrying out the faecal analysis of BB-12. The tablets were manufactured by Oy Karl Fazer Ab (Vantaa, Finland). The pacifiers were manufactured by Mekalasi Oy (Konnevesi, Finland). Neither Hansen, Fazer, or Mekalasi provided financial support for this clinical study. 1 author (TT) states "no conflict of interest". 1 author (CL) lists an affiliation with Chr. Hansen (which donated the BB-12 probiotics) in the author affiliations, but this is not noted in the COI. No information on COIs of the remaining authors.

Taipale 2016

Methods	NB: this study reports the results of a 2-year follow-up of the participants in Taipale 2011 (see above) Study design: 2-arm, placebo-controlled, randomised clinical study Method of randomisation: computer-generated randomisation list; blocks of 3 (see Taipale 2011) Blinding: double-blinded Duration: 2-year follow-up of participants in Taipale 2011 Exclusions postrandomisation: none Losses to follow-up: probiotic group: 17 did not receive tablet; control group: 17 did not receive tablet Non-adherence to protocol: probiotic group 6 (2 GI complaints, 4 arduousness of study); control group 2 (1 atopic eczema, 1 arduousness of study)
Participants	Country: Finland Setting: originally recruited via pamphlets at well-baby clinics Number of participants: randomised 109; probiotic 55, control 54 in original trial; this study reports on those participants who completed the 2-year follow up: 32 probiotics, 35 control Age: NR Inclusion criteria: the inclusion criteria of the Taipale 2011 trial were that: (1) the child was healthy, (2) the parents agreed to use the novel slow-release pacifier, and (3) the child started to use the pacifier before the age of 2 months. In cases where the child did not start using the pacifier but the parents were motivated to remain in the study, they were offered the possibility of delivering the crushed tablet to the child using a spoon. Reasons for not participating in the trial included moving out of the area, miscarriage, and lack of interest in the trial. Exclusion criteria: NR
Interventions	Treatment group: each probiotic tablet contained 5 billion CFU of *Bifidobacterium animalis* subsp. *lactis* BB-12, in addition to bulking agent xylitol. The smaller tablet contained 100 mg xylitol, whilst the larger tablet contained 300 mg xylitol. Test tablets were administered from the age of 1 to 2 months with a novel slow-release pacifier which contained a pouch in which the tablet was inserted. The children received the tablets twice a day via a small pacifier (volume 120 µL) until 6 to 8 months of age, thereafter via a larger pacifier (volume 250 µL) until the age of 2 years. Comparator group: the placebo tablet contained xylitol (the smaller tablet contained 100 mg xylitol, whilst the larger tablet contained 300 mg xylitol). The children received the tablets twice a day via a

Taipale 2016 *(Continued)*

	small pacifier (volume 120 µL) until 6 to 8 months of age, thereafter via a larger pacifier (volume 250 µL) until the age of 2 years.
Outcomes	Primary outcome(s): prevalence of overall acute infections occurring before the age of 2 years (ARTIs, AOM, GI, fever episodes) Secondary outcome(s): successful intestinal passage of BB-12
Notes	Authors' COIs: TJT was supported by a personal grant from Finnish Dental Society Apollonia. Disclosures: the authors declare that there are no conflicts of interest. Funding: Chr. Hansen A/S (Hoersholm, Denmark) donated the BB-12 and carried out the faecal analyses of BB-12. Oy Karl Fazer Ab (Vantaa, Finland) manufactured the tablets and Mekalasi Oy (Konnevesi, Finland) manufactured the pacifiers. Neither Hansen, Fazer, or Mekalasi provided financial support for this study. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list; blocks of 3
Allocation concealment (selection bias)	Unclear risk	NR
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All study personnel and participants were blinded to treatment assignment for the duration of the study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data were analysed with SPSS by a blinded statistician (KP).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons provided.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Authors' COIs: TJT was supported by a personal grant from Finnish Dental Society Apollonia. Disclosures: the authors declare that there are no conflicts of interest. Funding: Chr. Hansen A/S (Hoersholm, Denmark) donated the BB-12 and carried out the faecal analyses of BB-12. Oy Karl Fazer Ab (Vantaa, Finland) manufactured the tablets and Mekalasi Oy (Konnevesi, Finland) manufactured the pacifiers. Neither Hansen, Fazer, or Mekalasi provided financial support for this study. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Tano 2002

Methods	Study design: 2-arm, placebo-controlled, randomised clinical study

Tano 2002 *(Continued)*

	Method of randomisation: randomisation performed by a technician with no access to information about the included participants or the doctor involved; further details not reported Blinding: double-blinded Duration: 4 months Exclusions postrandomisation: none Losses to follow-up: probiotic: 3 did not complete the scheduled 4-month treatment; placebo: 1 did not complete the scheduled 4-month treatment Non-adherence to protocol: probiotic: 2 excluded due to freezer with alpha-haemolytic streptococci (AHS) suspension inadvertently being thawed; control: 1 excluded due to freezer with AHS suspension inadvertently being thawed
Participants	Country: Sweden Setting: children referred to ENT department due to recurrent AOM Number of participants: 43 "included" (not clear if this is the number randomised); probiotic 21, placebo 22 Age (mean, range): probiotic: 21.5 months (range 9 to 42), placebo: 20.7 months (range 4 to 46) Inclusion criteria: children referred to the ENT department in Boden and Umea because of recurrent AOM; aged 3 years and younger, and with a history of at least 3 episodes of AOM during the last 6 months or 6 episodes of AOM; aerated middle ears Exclusion criteria: patients with secretory otitis media in 1 or both ears; severe underlying diseases such as immunological deficiencies, valvular heart diseases, or wounds in the nose or mouth
Interventions	Treatment group: a suspension of 10% skim milk and 0.9% CFU/mL was used; strains included: 2 strains of *Streptococcus sanguis*, 2 strains of *S mitis*, 1 strain of *S oralis* in equal proportions. Spray once daily (1 puff 50 µL in each nostril) for 4 months. Comparator group: skim milk with 0.9% sodium chloride was used as a placebo control and was kept frozen until thawed and used. Spray once daily (1 puff 50 µL in each nostril) for 4 months.
Outcomes	Primary outcome(s): a reduction in AOM episodes (NB: this is not made explicit) Secondary outcome(s): not clear. Other outcomes reported in the article: URI episodes, AOM episodes, otalgia, serous otitis media (SOM), adverse events.
Notes	Authors' COIs: NR Funding: the present study was supported by the County Council of Norrbotten, the Joint Committee North Medical Care Region ('Visare Norr'), and the Swedish Medical Research Council (No. K2001-73x-06578-19A). Essum AB prepared the bottles with nasal spray. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by a technician with no access to information about included participants or doctor involved; baseline characteristics appear similar for both groups
Allocation concealment (selection bias)	Unclear risk	NR

Tano 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the investigator (KT) and the parents were blinded to the drug.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	NR
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition reported for both arms, with reasons provided.
Selective reporting (reporting bias)	Unclear risk	Outcomes not clearly identified.
Other bias	High risk	Authors' COIs: NR Funding: the present study was supported by the County Council of Norrbotten, the Joint Committee North Medical Care Region ('Visare Norr'), and the Swedish Medical Research Council (No. K2001-73x-06578-19A). Essum AB prepared of the bottles with nasal spray. The role of the funder (if any) in the conception, design, or conduct of the study or in the analysis or interpretation of the data was not reported.

AOM: acute otitis media
ARI: acute respiratory infection
CFU: colony-forming units
COI: conflict of interest
ENT: ear, nose, and throat
FEV1: forced expiratory volume in one second
GI: gastrointestinal
IL-8: interleukin-8
LRTI: lower respiratory tract infection
NR: not reported
SD: standard deviation
SOM: serous otitis media
TNF: tumour necrosis factor
URI: upper respiratory infection
URTI: upper respiratory tract infection

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Agustina 2012	Wrong outcomes
Ahanchian 2016	Wrong outcomes
Arvola 1999	Wrong outcomes
Aryayev 2012	Wrong outcomes
Auinger 2013	Wrong population
Bellomo 1980	Wrong outcomes

Study	Reason for exclusion
Canani 2016	Wrong outcomes
Cazzola 2010	Wrong outcomes
Cobo 2006	Wrong outcomes
Collet 1993	Wrong intervention
Corsello 2016	Wrong outcomes
Coulthard 2004	Wrong study type
Crawford 2015	Wrong study type
Cáceres 2010	Wrong outcomes
Dekker 2017	Wrong outcomes
Di Pierro 2012	Wrong study type
Garaiova 2015	Wrong outcomes
Gerasimov 2012	Wrong outcomes
Gerasimov 2016	Wrong outcomes
Gonchar 2015	Wrong outcomes
Guillemard 2010	Wrong population
Gutierrez-Castrellon 2014	Wrong outcomes
Hatakka 2001b	Wrong study type
He 2005	Wrong outcomes
Hojsak 2009a	Wrong outcomes
Hojsak 2009b	Wrong outcomes
Hojsak 2010b	Wrong outcomes
Hojsak 2015	Wrong outcomes
ISCTRN 2004	Clinical trial record only, picked up in literature searches; no publications resulting from this trial
Ito 2017	Wrong intervention
Jespersen 2015	Wrong population
Kaplan 1968	Wrong study type
Kloster 2008	Wrong outcomes

Study	Reason for exclusion
Kukkonen 2008	Wrong outcomes
Kumpu 2012	Wrong outcomes
Kumpu 2013	Wrong outcomes
Laursen 2017a	Wrong outcomes
Lehtoranta 2012	Wrong outcomes
Li 2014	Wrong outcomes
Lin 2009	Wrong outcomes
Luoto 2014	Wrong outcomes
Maldonado 2010	Wrong outcomes
Maldonado 2011	Wrong outcomes
Marchisio 2010	Wrong intervention
Marchisio 2016	Wrong study type
Marchisio 2017	Wrong study type
Marogna 2014	Wrong outcomes
Marseglia 2007	Wrong outcomes
Merenstein 2010	Wrong outcomes
Mizgier 2013	Wrong outcomes
Nocerino 2014	Wrong outcomes
Nocerino 2016	Wrong outcomes
Pitkaranta 2003	Conference abstract for a study that was included as a full article (Hatakka 2007a)
Prodeus 2016	Wrong outcomes
Puccio 2007	Wrong outcomes
Ringel-Kulka 2015	Wrong outcomes
Rivero 2004	Wrong outcomes
Río 2002	Wrong outcomes
Sazawal 2004	Wrong outcomes
Sazawal 2010	Wrong outcomes

Study	Reason for exclusion
Schrezenmeir 2004	Wrong outcomes
Skovbjerg 2009	Wrong outcomes
Smith 2016	Wrong outcomes
Stojkovic 2016	Wrong study type
Timby 2015	Wrong intervention
Vlieger 2009	Wrong outcomes
Weizman 2006	Wrong outcomes
West 2008	Wrong outcomes
Wright 2009	Wrong population

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12618000130268

Trial name or title	A randomised placebo controlled trial of the effect of BLIS probiotic, S. salivarius (K12) on otitis media (ear infections) and upper respiratory tract infections amongst 6-24 month old children, as measured by medical record events
Methods	Quadruple-blind (participant, individuals administering treatment, outcome assessors, outcome analysts), placebo-controlled, randomised clinical trial with 2 arms
Participants	Infants 6 months old; both genders
Interventions	Probiotic (*Streptococcus salivarius* K12), isomalt, maltodextrin, and natural flavour; placebo
Outcomes	The primary outcome will be rate of doctor-recorded AOM in the 18 months the child takes part in the trial.
Starting date	Not yet started; recruitment anticipated to start February 2018, actual start date not listed
Contact information	Prof Julian Crane, julian.crane@otago.ac.nz
Trial ID	ACTRN12618000130268
Trial name or title	BLIS-OM
Notes	-

EUCTR2017-000820-83-FI

Trial name or title	Otitis media and nasopharyngeal microbiome in children
Methods	Open, randomised clinical trial with 2 arms

EUCTR2017-000820-83-FI *(Continued)*

Participants	Age 1 to 6 years, in day-care centre in the city of Oulu, Finland
Interventions	*Streptococcus salivarius* K12 strain (oral powder in sachet); no treatment
Outcomes	Primary endpoint is the positive *S salivarius* quantitative 16S RNA PCR result in time points 1 and 2 months, e.g. after the 1 month use of the product and 1 month after that. Hence we are measuring the rate of *S salivarius* colonisation, or the microbiological efficiency of the different products. Samples are to be taken from controls as well since we do not know if the bacteria are able to transmit among children, and for how long the desired result lasts.
Starting date	Unclear. Current status: ongoing
Contact information	Oulu University Hospital, phone: +35883152011
Trial ID	EUCTR2017-000820-83-FI
Trial name or title	-
Notes	-

ISRCTN53286030

Trial name or title	A controlled trial of probiotics in the prevention of episodes of otitis media in general practice
Methods	Blinding NR, randomised, placebo-controlled trial
Participants	Children 6 to 11 months old, both genders
Interventions	Probiotics (*Lactobacillus* and bifidobacteria); placebo
Outcomes	Primary outcome: reported episodes of recurrent significant otalgia difference in proportions over 3 months
Starting date	September 2003
Contact information	Dr Ian Williamson, University of Southampton; igw@soton.ac.uk
Trial ID	ISRCTN53286030
Trial name or title	PIPO
Notes	-

NCT01724203

Trial name or title	Effect of 12-week probiotic supplementation on bacterial and viral infections in infants aged 6 to 12 months
Methods	Double-blind (participant, investigator), placebo-controlled, randomised clinical trial with 3 arms
Participants	Children aged 6 to 12 months, both genders

NCT01724203 *(Continued)*

Interventions	Arm 1: *Lactobacillus rhamnosus* HN001; arm 2: *Bifidobacterium animalis* subsp. *lactis*; arm 3: placebo
Outcomes	Primary outcome: proportion of participants with 1 or more of confirmed bacterial or viral infections at any time during the study
Starting date	December 2012
Contact information	Dr Xiaoyang Sheng, Xinhua Hospital, Shanghai Jiao Tong University School of Medicine (email/phone not provided)
Trial ID	NCT01724203
Trial name or title	-
Notes	-

NCT01909128

Trial name or title	Fermented milk and fermented rice on the appearance of respiratory and gastrointestinal symptoms
Methods	Quadruple-blind (participant, care provider, investigator, outcomes assessor), placebo-controlled, randomised clinical trial with 3 arms
Participants	Children aged 12 to 48 months, both genders
Interventions	Arm 1: fermented milk with probiotic; arm 2: fermented rice with probiotic; arm 3: placebo
Outcomes	Primary outcome: common respiratory and gastrointestinal infections
Starting date	February 2013
Contact information	Roberto Berni Canani, MD, PhD, Federico II University (email/phone not provided)
Trial ID	NCT01909128
Trial name or title	-
Notes	Included as Nocerino 2017

NCT02221687

Trial name or title	Evaluation of the efficacy and safety of an infant formula containing synbiotics and its effects on the incidence of infectious diseases in the infant gut: a double-blind, randomised, controlled interventional study
Methods	Triple-blind (participant, care provider, investigator), placebo-controlled, randomised clinical trial with 3 arms
Participants	Children up to 5 weeks old, both genders

NCT02221687 *(Continued)*

Interventions	Synbiotic formula (standard formula enriched with prebiotic + probiotic); control formula (standard formula); no intervention (breast fed group)
Outcomes	Primary outcome: cumulative number of infectious diarrhoea episodes per child during the first year of life
Starting date	August 2014
Contact information	Hugues Piloquet, Paediatrician (email/phone not provided)
Trial ID	NCT02221687
Trial name or title	GOLFIII
Notes	-

NCT02802059

Trial name or title	E. coli Nissle 1917 - suspension for infection prophylaxis
Methods	Double-blind (participant, investigator), placebo-controlled, randomised clinical trial with 2 arms
Participants	Age at inclusion: maximum 120 hours after birth, both genders
Interventions	*Escherichia coli* strain Nissle 1917 (EcN-Suspension) probiotic bacteria; placebo
Outcomes	Primary outcome: number of infections confirmed by a medical doctor
Starting date	October 2015
Contact information	Corinna Wolff, Dipl-Biophys; corinna.wolff@ardeypharm.de
Trial ID	NCT02802059
Trial name or title	RONi
Notes	-

NCT03516409

Trial name or title	Bio-Kult Infantis in AAD prevention in infants
Methods	Open, placebo-controlled, randomised clinical trial with 2 arms
Participants	Children 6 months to 35 months old, both genders
Interventions	Bio-Kult Infantis (a multistrain probiotic formula); placebo (maltodextrin DE19)
Outcomes	Primary outcome: incidence of antibiotic-associated diarrhoea
Starting date	April 2018

NCT03516409 *(Continued)*

Contact information	Dr Salvatore Tripodi, UOC Paediatric Hospital "Sandro Pertini" (email/phone not provided)
Trial ID	NCT03516409
Trial name or title	-
Notes	-

NCT03614117

Trial name or title	Effect of a new probiotic strain on recurrent acute otitis media in children
Methods	Quadruple-blind (participant, care provider, investigator, outcomes assessor), placebo-controlled, randomised clinical trial with 3 arms
Participants	Children 1 to 4 years old with recurrent AOM, and presence of AOM at the time of inclusion in the study
Interventions	Arm 1: *Lactobacillus salivarius* PS7 for 6 months; arm 2: *L salivarius* PS 7 + placebo for 3 months each; arm 3: placebo supplement
Outcomes	Primary outcome: number of AOM episodes
Starting date	October 2018
Contact information	Susana Manzano; susana.manzano@probisearch.com
Trial ID	NCT03614117
Trial name or title	PROMAR
Notes	-

AAD: antibiotic-associated diarrhoea
AOM: acute otitis media

NR: not reported
PCR: polymerase chain reaction
RNA: ribonucleic acid

DATA AND ANALYSES

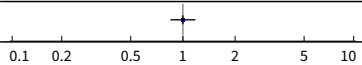
Comparison 1. Probiotics versus placebo or usual care

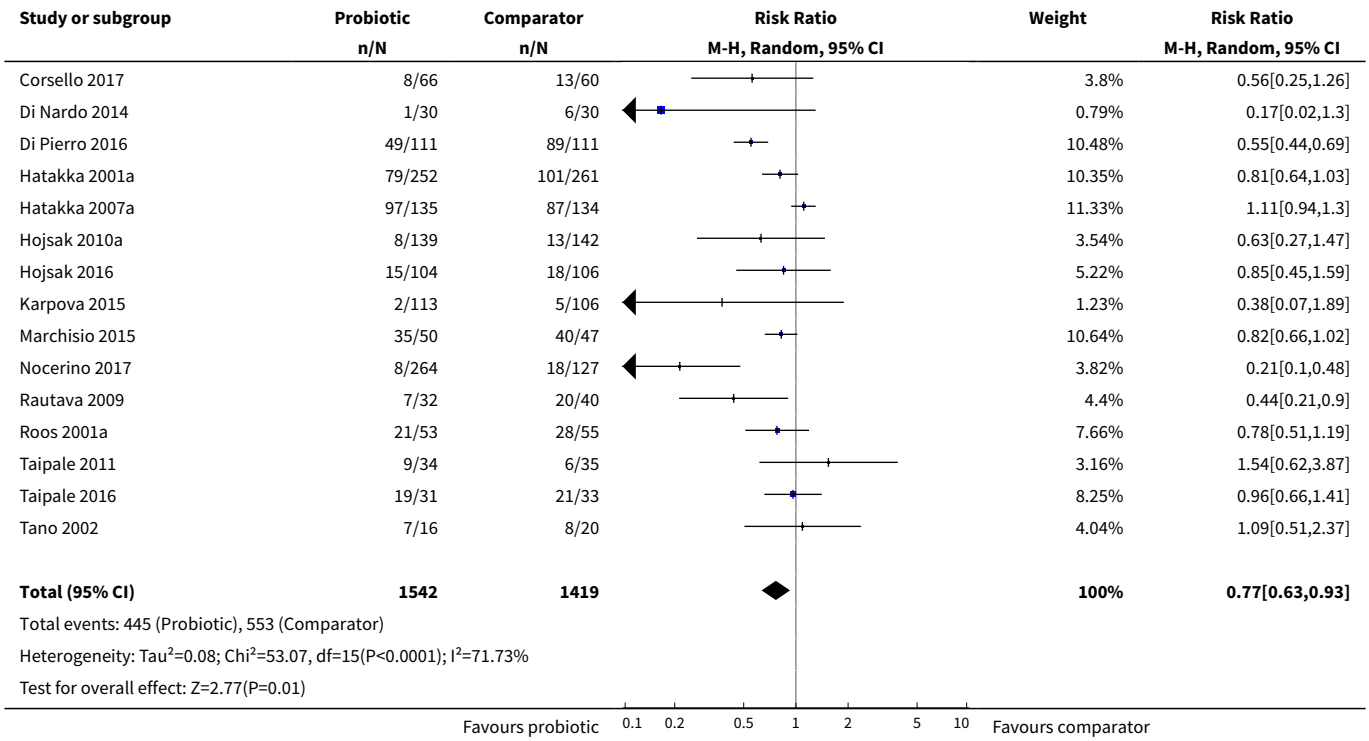
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of children with AOM (overall)	16	2961	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Proportion of children with AOM (by health status)	16	2961	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.93]
2.1 Children prone to otitis media	5	734	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.11]
2.2 Children not prone to otitis media	11	2227	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.49, 0.84]
3 Proportion of children with AOM (by probiotic strain)	16	2961	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.63, 0.93]
3.1 *Lactobacillus*-containing	10	2055	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.54, 0.98]
3.2 *Streptococcus*-containing	6	906	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.60, 1.02]
4 Adverse events	4	395	Odds Ratio (M-H, Random, 95% CI)	1.54 [0.60, 3.94]
5 Difference in the use of antibiotics	8	1768	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.51, 0.86]
5.1 Use of antibiotic for AOM	3	597	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.30, 1.32]
5.2 Use of antibiotic for other infections	5	1171	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.45, 0.92]
6 Time off school for the child (days)	5	1280	Mean Difference (IV, Random, 95% CI)	-0.95 [-2.47, 0.57]
7 Difference in proportion of children with other infections	11	3610	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.65, 0.87]
7.1 Acute respiratory infections	10	2167	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.88]
7.2 Gastrointestinal infections	8	1443	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.57, 1.06]
8 Compliance with taking probiotics	6	990	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.99, 1.05]

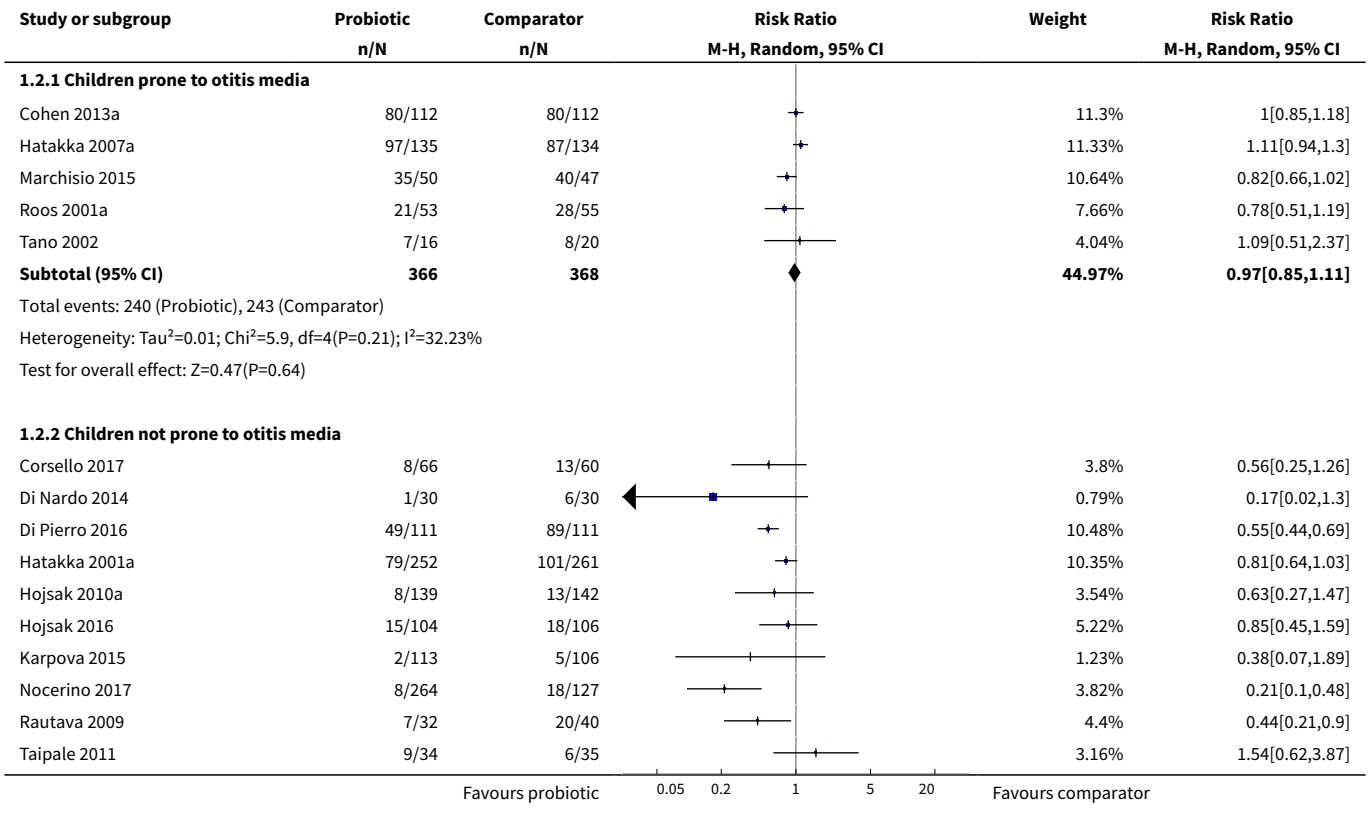
Analysis 1.1. Comparison 1 Probiotics versus placebo or usual care, Outcome 1 Proportion of children with AOM (overall).

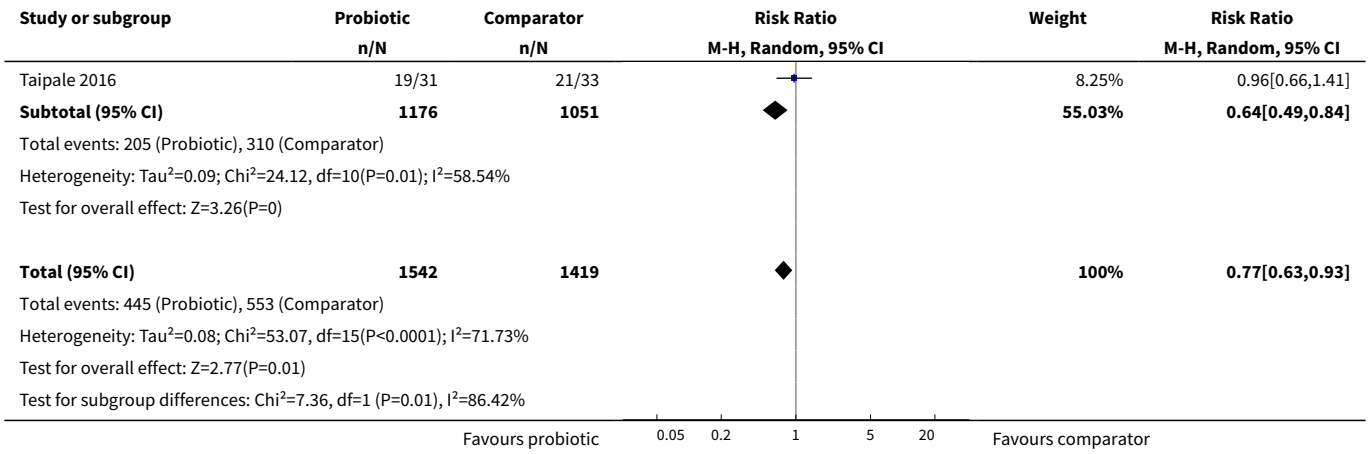
Study or subgroup	Probiotic n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Cohen 2013a	80/112	80/112		11.3%	1[0.85,1.18]



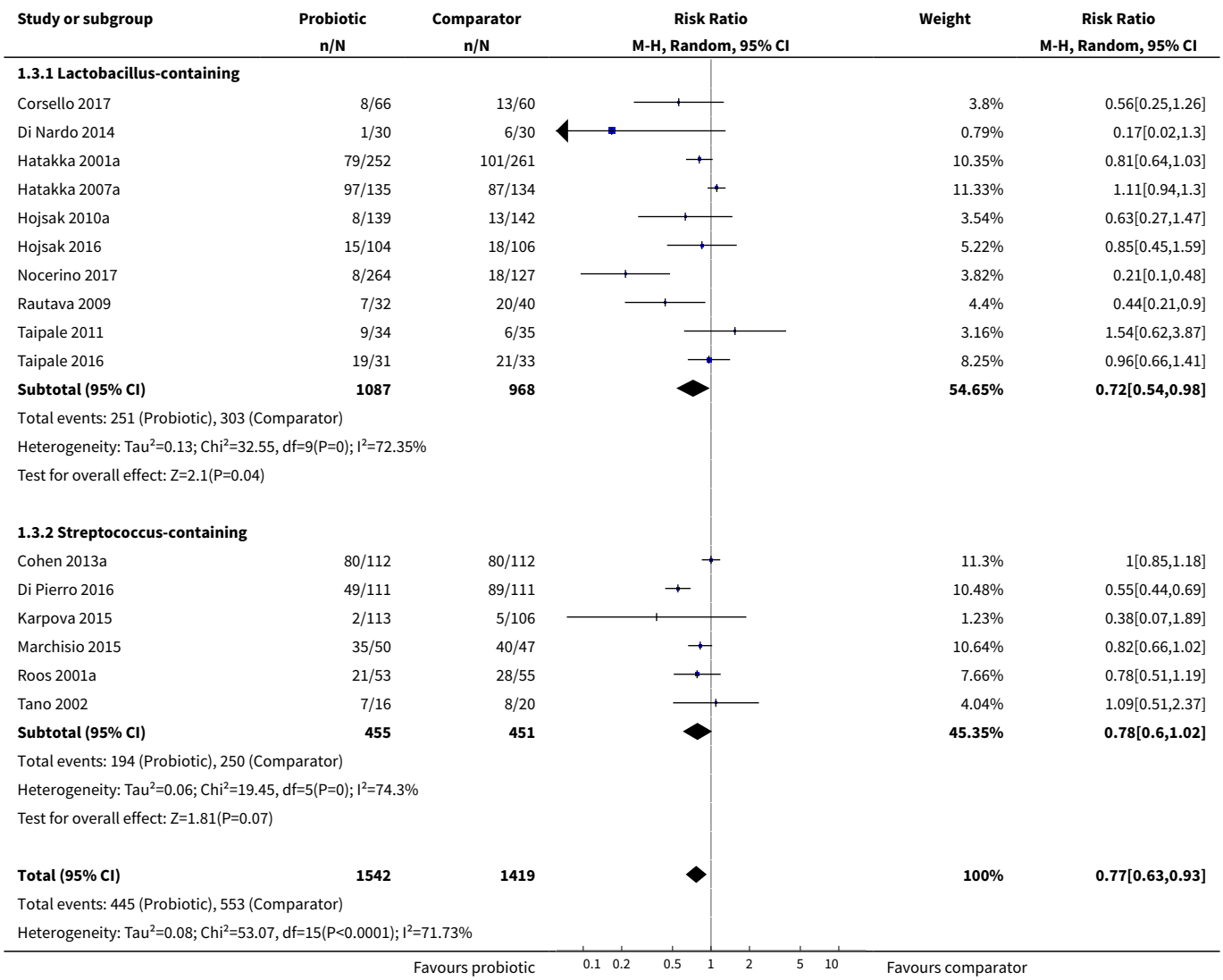


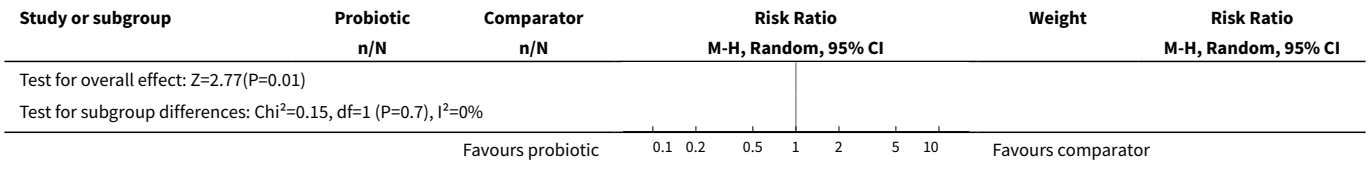
Analysis 1.2. Comparison 1 Probiotics versus placebo or usual care, Outcome 2 Proportion of children with AOM (by health status).



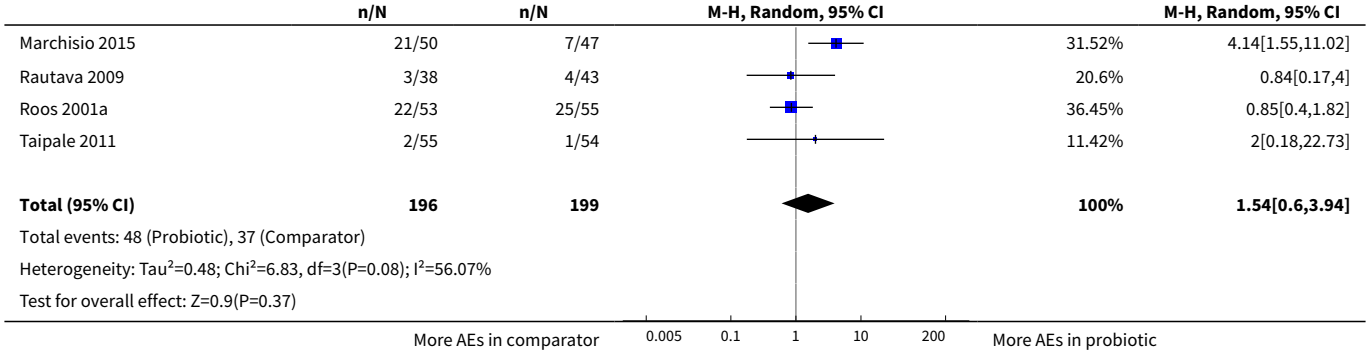


Analysis 1.3. Comparison 1 Probiotics versus placebo or usual care, Outcome 3 Proportion of children with AOM (by probiotic strain).

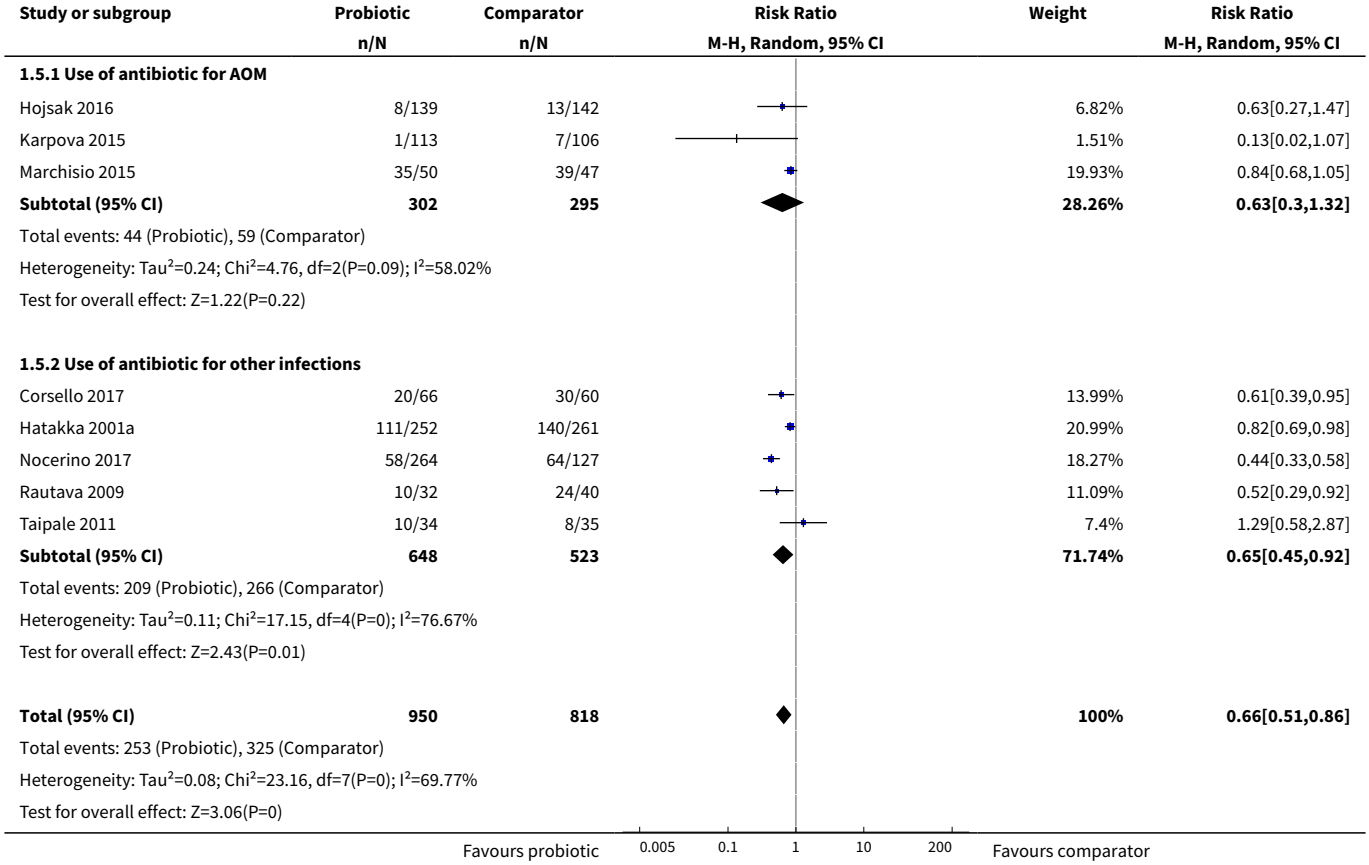




Analysis 1.4. Comparison 1 Probiotics versus placebo or usual care, Outcome 4 Adverse events.



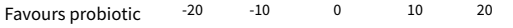
Analysis 1.5. Comparison 1 Probiotics versus placebo or usual care, Outcome 5 Difference in the use of antibiotics.



Study or subgroup	Probiotic n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: Chi²=0, df=1 (P=0.96), I²=0%					

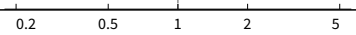
Analysis 1.6. Comparison 1 Probiotics versus placebo or usual care, Outcome 6 Time off school for the child (days).

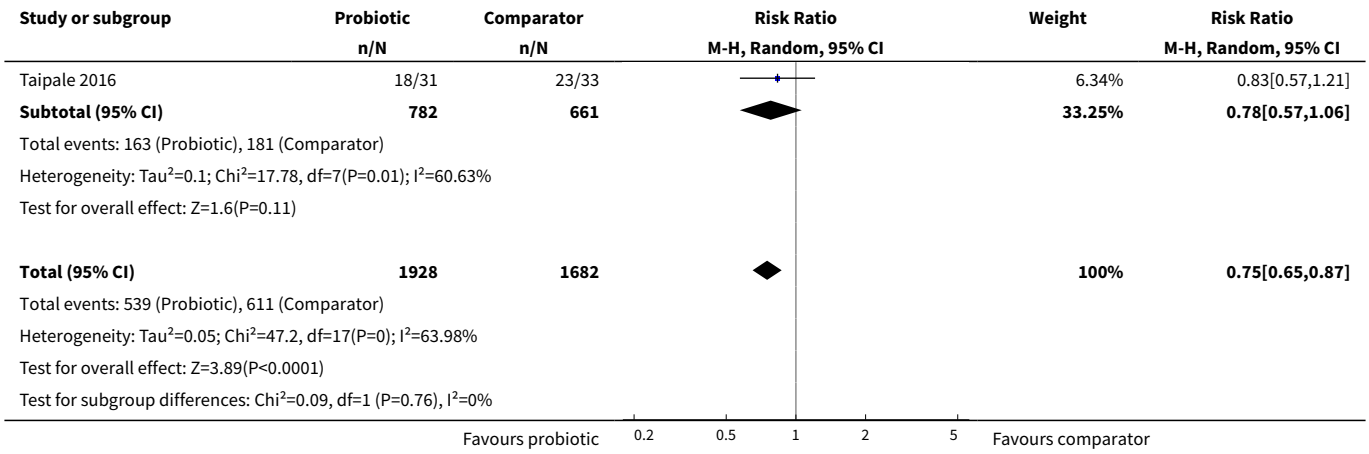
Study or subgroup	Probiotic N	Probiotic Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Corsello 2017	66	2 (4.1)	60	8 (15.8)		10.65%	-6[-10.12,-1.88]
Hatakka 2001a	252	4.9 (4.5)	261	5.8 (4.5)		43.34%	-0.9[-1.68,-0.12]
Hojsak 2010a	139	3.1 (63.2)	106	5.1 (70)		0.79%	-2[-18.97,14.97]
Hojsak 2016	104	4.5 (4)	106	4.2 (6)		34.89%	0.28[-1.1,1.66]
Stecksen-Blicks 2009	110	13.4 (12)	76	13.4 (15.8)		10.33%	0[-4.2,4.2]
Total * **	**671**		**609**			**100%**	**-0.95[-2.47,0.57]**
Heterogeneity: Tau²=1.23; Chi²=8.67, df=4(P=0.07); I²=53.87%							
Test for overall effect: Z=1.22(P=0.22)							



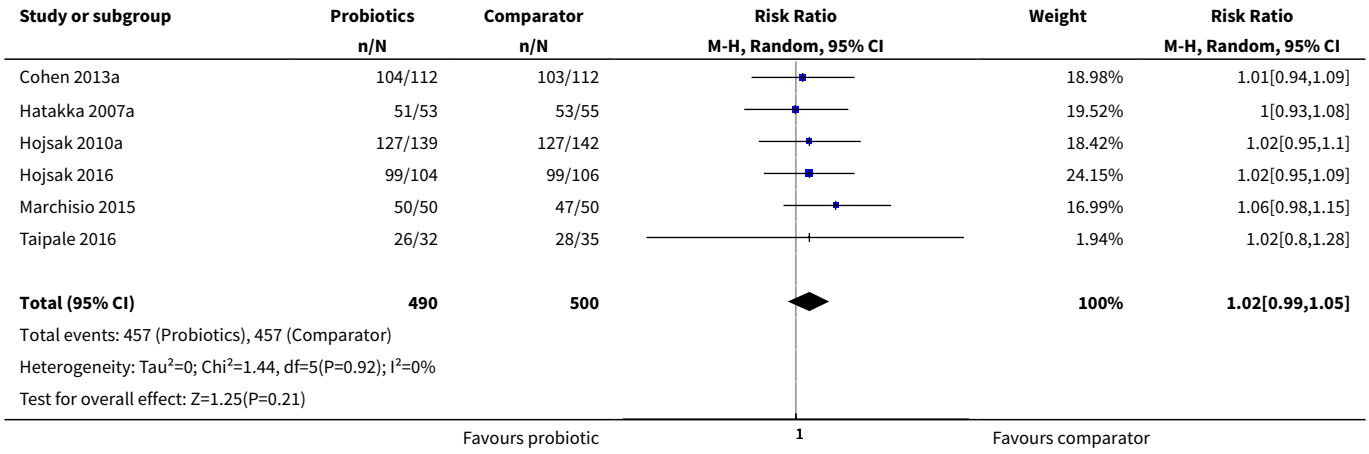
Analysis 1.7. Comparison 1 Probiotics versus placebo or usual care, Outcome 7 Difference in proportion of children with other infections.

Study or subgroup	Probiotic n/N	Comparator n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 Acute respiratory infections					
Corsello 2017	22/66	24/60		5.19%	0.83[0.53,1.32]
Di Pierro 2016	18/111	54/111		5.15%	0.33[0.21,0.53]
Hatakka 2001a	18/252	22/261		3.8%	0.85[0.47,1.54]
Hojsak 2010a	54/139	87/142		8.37%	0.63[0.5,0.81]
Hojsak 2016	44/104	43/106		7.14%	1.04[0.76,1.44]
Karpova 2015	4/113	14/106		1.53%	0.27[0.09,0.79]
Nocerino 2017	145/264	89/127		9.79%	0.78[0.67,0.92]
Rautava 2009	22/32	31/40		7.7%	0.89[0.67,1.18]
Taipale 2011	22/34	33/35		8.12%	0.69[0.53,0.89]
Taipale 2016	27/31	33/33		9.95%	0.87[0.75,1.01]
Subtotal (95% CI)	**1146**	**1021**		**66.75%**	**0.74[0.62,0.88]**
Total events: 376 (Probiotic), 430 (Comparator)					
Heterogeneity: Tau²=0.05; Chi²=30.3, df=9(P=0); I²=70.29%					
Test for overall effect: Z=3.48(P=0)					
1.7.2 Gastrointestinal infections					
Cohen 2013a	52/112	46/112		7.52%	1.13[0.84,1.52]
Corsello 2017	12/66	24/66		3.77%	0.5[0.27,0.91]
Hojsak 2010a	16/139	26/142		3.99%	0.63[0.35,1.12]
Hojsak 2016	14/104	11/106		2.81%	1.3[0.62,2.72]
Nocerino 2017	41/264	38/127		6.15%	0.52[0.35,0.76]
Rautava 2009	1/32	6/40		0.47%	0.21[0.03,1.64]
Taipale 2011	9/34	7/35		2.21%	1.32[0.56,3.15]





Analysis 1.8. Comparison 1 Probiotics versus placebo or usual care, Outcome 8 Compliance with taking probiotics.



APPENDICES

Appendix 1. Bibliographic database search strategies

PubMed (National Library of Medicine)

(Probiotics[Mesh] OR "Synbiotics"[Mesh] OR Lactobacillus[Mesh] OR Bifidobacterium[Mesh] OR Saccharomyces[Mesh] OR "Streptococcus thermophilus"[Mesh] OR "Cultured Milk Products"[Mesh] OR Antibiosis[Mesh] OR "Lactococcus"[Mesh] OR Probiotics[tiab] OR Probiotic[tiab] OR Synbiotics[tiab] OR Synbiotic[tiab] OR Lactobacillus[tiab] OR Lactobacilli[tiab] OR Bifidobacteria[tiab] OR Bifidobacterium[tiab] OR Saccharomyces[tiab] OR Saccharomyce[tiab] OR “Microbial dietary supplements”[tiab] OR Yoghurt[tiab] OR “Fermented milk”[tiab] OR “Cultured Milk”[tiab] OR “Fermented Dairy”[tiab] OR Acidophilus[tiab] OR Antibiosis[tiab] OR “Microbial Antagonism”[tiab] OR “Microbial Antagonisms”[tiab] OR “Bacterial Interferences”[tiab] OR “Bacterial Interference”[tiab] OR "Streptococcus thermophilus"[tiab] OR “Bacillus laterosporus”[tiab] OR “Pediococcus acidilactici”[tiab] OR Lactococcus[tiab] OR Lactis[tiab])

AND

("Respiratory Tract Infections"[Mesh] OR "Respiratory tract infection"[tiab] OR "Respiratory tract infections"[tiab] OR "Respiratory infection"[tiab] OR "Respiratory infections"[tiab] OR urti[tiab] OR uri[tiab] OR ari[tiab] OR "Otitis Media"[Mesh] OR "Otitis Media"[tiab]

OR “Glue ear”[tiab] OR AOM[tiab] OR OME[tiab] OR (“Middle Ear”[tiab] AND (Infection[tiab] OR Infections[tiab] OR Inflammation[tiab] OR Inflammations[tiab])))

AND

((Randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR "drug therapy"[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab])

NOT

(Animals[Mesh] not (Animals[Mesh] and Humans[Mesh])))

CENTRAL (Cochrane Central Register of Controlled Trials)

([mh Probiotics] OR [mh Synbiotics] OR [mh Lactobacillus] OR [mh Bifidobacterium] OR [mh Saccharomyces] OR [mh "Streptococcus thermophilus"] OR [mh "Cultured Milk Products"] OR [mh Antibiosis] OR [mh Lactococcus] OR Probiotics:ti,ab OR Probiotic:ti,ab OR Synbiotics:ti,ab OR Synbiotic:ti,ab OR Lactobacillus:ti,ab OR Lactobacilli:ti,ab OR Bifidobacteria:ti,ab OR Bifidobacterium:ti,ab OR Saccharomyces:ti,ab OR Saccharomyce:ti,ab OR "Microbial dietary supplements":ti,ab OR Yoghurt:ti,ab OR "Fermented milk":ti,ab OR "Cultured Milk":ti,ab OR "Fermented Dairy":ti,ab OR Acidophilus:ti,ab OR Antibiosis:ti,ab OR "Microbial Antagonism":ti,ab OR "Microbial Antagonisms":ti,ab OR "Bacterial Interferences":ti,ab OR "Bacterial Interference":ti,ab OR "Streptococcus thermophilus":ti,ab OR "Bacillus laterosporus":ti,ab OR "Pediococcus acidilactici":ti,ab OR Lactococcus:ti,ab OR Lactis:ti,ab)

AND

([mh "Respiratory Tract Infections"] OR "Respiratory tract infection":ti,ab OR "Respiratory tract infections":ti,ab OR "Respiratory infection":ti,ab OR "Respiratory infections":ti,ab OR urti:ti,ab OR uri:ti,ab OR ari:ti,ab OR [mh "Otitis Media"] OR "Otitis Media":ti,ab OR "Glue ear":ti,ab OR AOM:ti,ab OR OME:ti,ab OR ("Middle Ear":ti,ab AND (Infection:ti,ab OR Infections:ti,ab OR Inflammation:ti,ab OR Inflammations:ti,ab)))

Embase (via Elsevier)

('probiotic agent'/exp OR 'synbiotic agent'/exp OR 'Lactobacillus'/exp OR 'Bifidobacterium'/exp OR 'Saccharomyces'/exp OR 'Streptococcus thermophilus'/exp OR 'fermented milk product'/exp OR 'Antibiosis'/exp OR 'Lactococcus'/exp OR Probiotics:ti,ab OR Probiotic:ti,ab OR Synbiotics:ti,ab OR Synbiotic:ti,ab OR Lactobacillus:ti,ab OR Lactobacilli:ti,ab OR Bifidobacteria:ti,ab OR Bifidobacterium:ti,ab OR Saccharomyces:ti,ab OR Saccharomyce:ti,ab OR "Microbial dietary supplements":ti,ab OR Yoghurt:ti,ab OR "Fermented milk":ti,ab OR "Cultured Milk":ti,ab OR "Fermented Dairy":ti,ab OR Acidophilus:ti,ab OR Antibiosis:ti,ab OR "Microbial Antagonism":ti,ab OR "Microbial Antagonisms":ti,ab OR "Bacterial Interferences":ti,ab OR "Bacterial Interference":ti,ab OR "Streptococcus thermophilus":ti,ab OR "Bacillus laterosporus":ti,ab OR "Pediococcus acidilactici":ti,ab OR Lactococcus:ti,ab OR Lactis:ti,ab)

AND

('respiratory tract infection'/exp OR "Respiratory tract infection":ti,ab OR "Respiratory tract infections":ti,ab OR "Respiratory infection":ti,ab OR "Respiratory infections":ti,ab OR urti:ti,ab OR uri:ti,ab OR ari:ti,ab OR 'Otitis Media'/exp OR "Otitis Media":ti,ab OR "Glue ear":ti,ab OR AOM:ti,ab OR OME:ti,ab OR ("Middle Ear":ti,ab AND (Infection:ti,ab OR Infections:ti,ab OR Inflammation:ti,ab OR Inflammations:ti,ab)))

AND

(random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp)))

AND

[embase]/lim

CINAHL

((MH "Probiotics+") OR (MH "Lactobacillus+") OR (MH "Bifidobacterium+") OR (MH "Saccharomyces+") OR (MH "Streptococcus+") OR (MH "Cultured Milk Products+") OR (MH "Antibiosis+") OR TI Probiotics OR AB Probiotics OR TI Probiotic OR AB Probiotic OR TI Synbiotics OR AB Synbiotics OR TI Synbiotic OR AB Synbiotic OR TI Lactobacillus OR AB Lactobacillus OR TI Lactobacilli OR AB Lactobacilli OR TI Bifidobacteria OR AB Bifidobacteria OR TI Bifidobacterium OR AB Bifidobacterium OR TI Saccharomyces OR AB Saccharomyces OR TI Saccharomyce OR AB Saccharomyce OR TI "Microbial dietary supplements" OR AB "Microbial dietary supplements" OR TI Yoghurt OR AB Yoghurt OR TI "Fermented milk" OR AB "Fermented milk" OR TI "Cultured Milk" OR AB "Cultured Milk" OR TI "Fermented Dairy" OR AB "Fermented Dairy" OR TI Acidophilus OR AB Acidophilus OR TI Antibiosis OR AB Antibiosis OR TI "Microbial Antagonism" OR AB "Microbial Antagonism" OR TI "Microbial Antagonisms" OR AB "Microbial Antagonisms" OR TI "Bacterial Interferences" OR AB "Bacterial Interferences"

OR TI "Bacterial Interference" OR AB "Bacterial Interference" OR TI "Streptococcus thermophilus" OR AB "Streptococcus thermophilus" OR TI "Bacillus laterosporus" OR AB "Bacillus laterosporus" OR TI "Pediococcus acidilactici" OR AB "Pediococcus acidilactici" OR TI Lactococcus OR AB Lactococcus OR TI Lactis OR AB Lactis)

AND

((MH "Respiratory Tract Infections+") OR TI "Respiratory tract infection" OR AB "Respiratory tract infection" OR TI "Respiratory tract infections" OR AB "Respiratory tract infections" OR TI "Respiratory infection" OR AB "Respiratory infection" OR TI "Respiratory infections" OR AB "Respiratory infections" OR TI urti OR AB urti OR TI uri OR AB uri OR TI ari OR AB ari OR (MH "Otitis Media+") OR TI "Otitis Media" OR AB "Otitis Media" OR TI "Glue ear" OR AB "Glue ear" OR TI AOM OR AB AOM OR TI OME OR AB OME OR (TI "Middle Ear" OR AB "Middle Ear" AND (TI Infection OR AB Infection OR TI Infections OR AB Infections OR TI Inflammation OR AB Inflammation OR TI Inflammations OR AB Inflammations)))

AND

((MH "Clinical Trials+") OR (MH "Quantitative Studies") OR TI placebo* OR AB placebo* OR (MH "Placebos") OR (MH "Random Assignment") OR TI random* OR AB random* OR TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR TI clinic* trial* OR AB clinic* trial* OR PT clinical trial)

Web of Science

(Probiotics OR Synbiotics OR Lactobacillus OR Bifidobacterium OR Saccharomyces OR "Streptococcus thermophilus" OR "Cultured Milk Products" OR Antibiosis OR Lactococcus OR Probiotics OR Probiotic OR Synbiotics OR Synbiotic OR Lactobacillus OR Lactobacilli OR Bifidobacteria OR Bifidobacterium OR Saccharomyces OR Saccharomyce OR "Microbial dietary supplements" OR Yoghurt OR "Fermented milk" OR "Cultured Milk" OR "Fermented Dairy" OR Acidophilus OR Antibiosis OR "Microbial Antagonism" OR "Microbial Antagonisms" OR "Bacterial Interferences" OR "Bacterial Interference" OR "Streptococcus thermophilus" OR "Bacillus laterosporus" OR "Pediococcus acidilactici" OR Lactococcus OR Lactis)

AND

("Respiratory Tract Infections" OR "Respiratory tract infection" OR "Respiratory tract infections" OR "Respiratory infection" OR "Respiratory infections" OR urti OR uri OR ari OR "Otitis Media" OR "Otitis Media" OR "Glue ear" OR AOM OR OME OR ("Middle Ear" AND (Infection OR Infections OR Inflammation OR Inflammations)))

AND

(TS=(random* or placebo* or allocat* or crossover* or "cross over" or ((singl* or doubl*) NEAR/1 blind*)) OR TI=(trial))

LILACS

(Probiotics OR Synbiotics OR Lactobacillus OR Bifidobacterium OR Saccharomyces OR "Streptococcus thermophilus" OR "Cultured Milk Products" OR Antibiosis OR Lactococcus OR Probiotics OR Probiotic OR Synbiotics OR Synbiotic OR Lactobacillus OR Lactobacilli OR Bifidobacteria OR Bifidobacterium OR Saccharomyces OR Saccharomyce OR "Microbial dietary supplements" OR Yoghurt OR "Fermented milk" OR "Cultured Milk" OR "Fermented Dairy" OR Acidophilus OR Antibiosis OR "Microbial Antagonism" OR "Microbial Antagonisms" OR "Bacterial Interferences" OR "Bacterial Interference" OR "Streptococcus thermophilus" OR "Bacillus laterosporus" OR "Pediococcus acidilactici" OR Lactococcus OR Lactis)

AND

("Respiratory Tract Infections" OR "Respiratory tract infection" OR "Respiratory tract infections" OR "Respiratory infection" OR "Respiratory infections" OR urti OR uri OR ari OR "Otitis Media" OR "Otitis Media" OR "Glue ear" OR AOM OR OME OR ("Middle Ear" AND (Infection OR Infections OR Inflammation OR Inflammations)))

AND

(random* or placebo* or allocat* or crossover* or "cross over" or blind* OR trial)

Appendix 2. Trial registry search strategies

ClinicalTrials.gov

(Probiotics OR Probiotic OR Synbiotics OR Synbiotic OR Lactobacillus OR Lactobacilli OR milk OR Acidophilus OR Yoghurt) AND ("Otitis Media" OR "Glue ear" OR AOM OR OME OR "Middle Ear Infection")

WHO ICTRP

Probiotics AND "Otitis Media" OR Probiotic AND "Otitis Media" OR Synbiotics AND "Otitis Media" OR Synbiotic AND "Otitis Media" OR Lactobacillus AND "Otitis Media" OR Lactobacilli AND "Otitis Media" OR milk AND "Otitis Media" OR Acidophilus AND "Otitis Media" OR Yoghurt AND "Otitis Media"

CONTRIBUTIONS OF AUTHORS

Draft the protocol: AMS, KG, Elaine Beller, KR, JC, PL, CDM
Develop the search strategy: JC
Run the search strategy: JC
Obtain copies of trials: JC
Select which trials to include: AMS, JC, FI, BJ
Extract data from trials: AMS, FI, BJ
Enter data into Review Manager 5: AMS
Carry out the analysis: AMS, CDM
Interpret the analysis: AMS, JC, BJ, FI, KR, KG, PL, CDM
Draft the final review: AMS, KG, CDM
Update the review: AMS, CDM

DECLARATIONS OF INTEREST

Anna M Scott: Salary funded by the Centre for Research Excellence in Minimising Antibiotic Resistance from Acute Respiratory Infections (CREMARA), which itself is funded by the National Health and Medical Research Council (NHMRC), Australia.

Justin Clark: Salary funded by the Centre for Research Excellence in Minimising Antibiotic Resistance from Acute Respiratory Infections (CREMARA), which itself is funded by the National Health and Medical Research Council (NHMRC), Australia.

Blair Julien: has no conflicts of interest to declare.

Farhana Islam: has no conflicts of interest to declare.

Kristian Roos: is a minor shareholder of a small biomedical company (ESSUM AB), which has for many years been performing research with probiotic bacteria. ESSUM AB has no patent in probiotic bacteria that might be used for acute otitis media, and ESSUM has no intention of conducting research into acute otitis media.

Keith Grimwood: has no conflicts of interest to declare.

Paul Little: A study for which PL was Chief Investigator had placebo and probiotic tablets provided by a commercial company that makes probiotic (Cultech).

Chris Del Mar: reports Centre for Research Excellence in Minimising Antibiotic Resistance from Acute Respiratory Infections (CREMARA) and Centre of Research in Minimising Antibiotic Resistance in the Community (CRE-MARC) institutional funding (National Health and Medical Research Council (NHMRC)); Cochrane Acute Respiratory Infections Group institutional funding (NHMRC); institutional and personal funding from the Australian Commission on Safety and Quality in Health Care for the development of patient decision aids; personal consulting funding for shared decision-making implementation (BUPA, UK); American College of Physicians (ACP) Journal Club editorial work; consultancy/providing advice to a pharmaceutical company about a proposed vaccine that might be effective against otitis media in children.

SOURCES OF SUPPORT

Internal sources

- There are no internal sources of support to report, Other.

External sources

- There are no external sources of support to report, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences from the protocol:

1. Study population: the protocol stated that the population of interest is children (aged ≤ 18 years) diagnosed with acute otitis media (AOM) by a clinician. Because this review looks at the role of probiotics in preventing AOM, we broadened the population to include any children (aged ≤ 18 years), still including children diagnosed with AOM.

2. Electronic searches: the protocol stated that we would contact trial investigators for unpublished data. The status of trials categorised as 'ongoing studies' is as follows: not yet started or ongoing (five trials); contact information not available (two trials); already published (publication included in the present review) (one trial); awaiting response from investigators (one trial) (ISRCTN53286030).
3. Electronic searches: our protocol specified that we would use the 'similar articles' feature in PubMed and shared citation matcher in Web of Science. However, as forward and backward citation searches did not yield any additional included trials, we did not expect to find any additional included trials this way.
4. Subgroup analysis: we planned to carry out the following subgroup analyses: (1) child's age (≤ two years old), (2) type of probiotic, (3) children with severe AOM, (4) trials that included a co-intervention. (1) The first subgroup analysis was planned because the initial Population Intervention Comparison Outcome (PICO) stated that included trials will have as their population children diagnosed with AOM, and there is no consensus on the benefit of antibiotics in AOM in children younger than two years old and guidelines recommend selective use of antibiotics for AOM in children older than two years old (Rovers 2006). As the population was amended to include all children, this subgroup analysis was omitted. (2) We did conduct an analysis by probiotic type (see Analysis 1.3). (3) We did not conduct a subgroup analysis by severity of AOM, as this outcome was reported by only one included trial. (4) We did not conduct a subgroup analysis by co-intervention because in only one trial all children (both groups) received a co-intervention (Roos 2001a).
5. Sensitivity analysis: we planned to carry out a sensitivity analysis on including versus excluding trials with two or more domains rated as at high risk of bias, however this was not performed as only one included study rated two domains as at high risk of bias.
6. Primary outcome was specified as 'incidence of AOM' in the protocol. This was reported as 'proportion of children with AOM' in the review due to variation in the time points at which studies reported the outcome.
7. Secondary outcome was specified as 'difference between probiotic and non-probiotic groups in use of antibiotics to treat AOM (e.g. dose, duration)' in the protocol. This was reported as 'difference in the use of antibiotics' in the review to more accurately refect the evidence available for meta-analyses.
8. 'Summary of findings' table: the protocol stated that we would create a 'Summary of findings' table using the following outcomes: incidence of AOM, severity of AOM, adverse events, median duration of AOM episodes, difference between groups in antibiotic use, time off school (child), time off work (parent or carer). Due to a paucity of data and change in how the primary outcome was reported (proportion of children with AOM), we instead reported the following outcomes: proportion of children with AOM, proportion of children with AOM among children not prone to AOM, proportion of children with AOM among children prone to AOM, severity of AOM, adverse events, time off school for child, difference in antibiotic use, difference in proportion of children with other infections.
9. Three subgroup analyses were not prespecified but were conducted because there were sufficient data available for pooling: difference in the use of antibiotics (subgroups: for AOM, for other infections); difference in other infections (subgroups: reduction in acute respiratory infections, reduction in gastrointestinal infections); and proportion of children with AOM (children prone to AOM, children not prone to AOM).
10. Authorship: one of the protocol authors (Elaine Beller) was not involved in the systematic review itself and is thus not listed as an author here.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [therapeutic use]; Disease Susceptibility; Otitis Media [epidemiology] [*prevention & control]; Probiotics [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic [statistics & numerical data]

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant